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(54)名稱

抑制抑制素亞基βE（INHBE）的表達的組合物和方法

(57)摘要

本發明提供了用於降低 INHBE 基因的表達並且用於治療 INHBE 相關疾病和病症的組合物和方法。提供了可用於降低細胞和受試者的 INHBE 表達的 INHBE dsRNA 藥劑、INHBE 反義多核苷酸藥劑、包含 INHBE dsRNA 藥劑的組合物和包含 INHBE 反義多核苷酸藥劑的組合物。

【發明摘要】

【中文發明名稱】　抑制抑制素亞基βE（INHBE）的表達的組合物和方法

【英文發明名稱】 COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF INHIBIN SUBUNIT BETA E (INHBE)

【中文】

本發明提供了用於降低 INHBE 基因的表達並且用於治療 INHBE 相關疾病和病症的組合物和方法。提供了可用於降低細胞和受試者的 INHBE 表達的 INHBE dsRNA 藥劑、INHBE 反義多核苷酸藥劑、包含 INHBE dsRNA 藥劑的組合物和包含 INHBE 反義多核苷酸藥劑的組合物。

【指定代表圖】　無

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】　抑制抑制素亞基βE（INHBE）的表達的組合物和方法

【英文發明名稱】 COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF INHIBIN SUBUNIT BETA E (INHBE)

【技術領域】

【0001】 本發明部分地涉及可用於抑制抑制素亞基βE（INHBE）基因表達的組合物和方法。

【先前技術】

【0002】 抑制素亞基βE（INHBE）是一種屬於轉化生長因子-β（TGF-β）家族的生長因子。INHBE mRNA主要在肝臟中表達，並且INHBE參與對肝臟細胞生長和分化的調節。抑制素還涉及調節許多細胞過程，包括細胞增殖、細胞凋亡、免疫應答和激素分泌。抑制素和活化素分別抑制和激活垂體腺分泌促卵泡激素。抑制素/活化素參與調節幾種不同的功能，諸如下丘腦和垂體激素分泌、性腺激素分泌、生殖細胞發育和成熟、紅細胞系分化、胰島素分泌、神經細胞存活、胚胎軸發育或骨骼生長，這取決於它們的亞基組成。抑制素似乎與活化素的功能相反。此外，INHBE可在內質網應激條件下被上調，並且該蛋白質可抑制胰腺和肝臟中的細胞增殖和生長。此外，先前的研究報導了抑制素βE（INHBE）被鑒定為一種新的推定的肝臟因子，其具有與胰島素抵抗和與人體脂肪相關的代謝病症呈正相關

的肝基因表達。另外，INHBE基因表達在糖尿病小鼠（2型糖尿病的齧齒類動物模型）的肝臟中增加。

【0003】 體脂肪分佈是與整體肥胖無關的心血管和代謝疾病的重要風險因素。與體脂肪分佈相關的代謝病症包括但不限於：2型糖尿病、高脂血症或血脂異常（低密度脂蛋白膽固醇（LDL-C）、甘油三酯、極低密度脂蛋白膽固醇（VLDL-C）、載脂蛋白B或其他脂質成分的循環水平高或改變）、肥胖症（特別是腹部肥胖症）、脂肪代謝障礙（諸如無法在區域性脂肪庫中沉積脂肪（部分脂肪代謝障礙）或者無法在全身沉積脂肪（脂肪萎縮））、胰島素抵抗或者在空腹時或在代謝挑戰期間的胰島素水平較高或改變、肝臟脂肪沉積或脂肪肝病及其併發症（諸如，例如肝硬化、纖維化或肝臟炎症）、非酒精性脂肪性肝炎、其他類型的肝臟炎症、肝酶水平或其他肝損傷標誌物較高或升高或改變、肝臟中的炎症或脂肪沉積、血壓較高和/或高血壓症、血糖或葡萄糖較高或高血糖症、代謝症候群、冠狀動脈疾病和其他動脈粥樣硬化病症，以及上述病症中的每一者的併發症。鑒定與更有利的脂肪分佈（諸如較低的WHR，特別是當針對BMI進行校正時）相關的遺傳變體，可作為一種鑒定在治療這些心臟代謝疾病中可帶來獲益的機制的途徑。

【0004】 因此，本領域中存在用於抑制INHBE表達和/或活性的本文公開的INHBE基因RNAi藥劑，從而為患有代謝障礙諸如代謝症候群和相關疾病（例如糖尿病、高血壓症和心血管疾病）的受試者提供替代治療。

【發明內容】

【0005】 總體而言，本公開內容提供了新型抑制素亞基βE（INHBE）基因特異性RNAi藥劑、包含INHBE RNAi藥劑的組合物，以及使用該INHBE RNAi藥劑和包含本文所述的INHBE RNAi藥劑的組合物在體外和/或體內抑制INHBE基因的表達的方法。本文所述的INHBE RNAi藥劑可選擇性地且有效地減少、抑制或沉默受試者（例如人或動物受試者）體內INHBE基因的表達。

【0006】 根據本發明的一個方面，提供了一種用於抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈包含與SEQ ID NO: 1、3、5或7的核苷酸序列相差不超過1、2、3個核苷酸的至少15個連續核苷酸，並且該反義鏈包含與SEQ ID NO: 2、4、6或8的核苷酸序列相差不超過1、2、3個核苷酸的至少15個連續核苷酸，其中該有義鏈和該反義鏈彼此能夠部分地、基本上或完全互補。

【0007】 在一些實施方案中，該dsRNA藥劑包含形成雙鏈區的有義鏈和反義鏈，其中所述反義鏈包含與INHBE RNA轉錄本互補的區域，該區域包含與表1至表3中的任一個表中列出的反義序列中的任一者相差不超過1、2、或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸。在一些實施方案中，該dsRNA藥劑包含形成雙鏈區的有義鏈和反義鏈，其中所述反義鏈包含與INHBE RNA轉錄本互補的區域，該區域包含來自表1至表3中的任一個表中列出的反義序列中的任一者的至少15、16、17、18、19、20或21個連續核苷酸。

【0008】 在一些實施方案中，該dsRNA藥劑包含有義鏈和反義鏈，該反義鏈中的核苷酸位置2至18包含與INHBE RNA轉錄本互補的區域，該區

域具有與表1至表3中的一個表中列出的反義序列之一相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，並且任選地包含靶向配體。

【0009】 在一些實施方案中，提供了一種抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈包含與SEQ ID NO: 1的核苷酸351-381、361-391、398-428、520-550、521-551、554-584、576-606、619-649、625-655、627-657、628-658、629-659、631-661、632-662、633-663、639-669、742-772、761-791、763-793、766-796、768-798、769-799、775-805、776-806、777-807、778-808、779-809、780-810、783-813、785-815、817-847、875-905、876-906、883-913、884-914、950-980、951-981、974-1004、975-1005、981-1011、982-1012、1032-1062、1035-1065、1092-1122、1093-1123、1094-1124、1095-1125、1102-1132、1116-1146、1126-1156、1127-1157、1141-1171、1196-1226、1197-1227、1198-1228、1200-1230、1207-1237、1208-1238、1209-1239、1213-1243、1215-1245、1230-1260、1237-1267、1265-1295、1278-1308、1296-1326、1298-1328、1299-1329、1302-1332、1304-1334、1305-1335、1308-1338、1344-1374、1381-1411、1382-1412、1383-1413、1389-1419、1390-1420、1391-1421、1393-1423、1399-1429、1424-1454、1425-1455、1426-1456、1427-1457、1428-1458、1430-1460、1431-1461、1432-1462、1434-1464、1457-1487、1461-1491、1497-1527、1600-1630、1607-1637、1608-1638、1609-1639、1641-1671、1643-1673、1644-1674、1661-1691、1781-1811、1803-1833、1805-1835、1806-

1836、1844-1874、1852-1882、1856-1886、1857-1887、1859-1889、1860-1890、1861-1891、2021-2051、2157-2187、2158-2188、2160-2190、2161-2191、2162-2192、2170-2200、2171-2201的核苷酸序列中的任一者相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，並且該反義鏈包含與SEQ ID NO: 2的對應核苷酸序列相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，其中該有義鏈和該反義鏈彼此能夠部分地、基本上或完全互補。

【0010】 在一些實施方案中，提供了一種抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈包含與SEQ ID NO: 1的核苷酸354-378、364-388、401-425、523-547、524-548、557-581、579-603、622-646、628-652、630-654、631-655、632-656、634-658、635-659、636-660、642-666、745-769、764-788、766-790、769-793、771-795、772-796、778-802、779-803、780-804、781-805、782-806、783-807、786-810、788-812、820-844、878-902、879-903、886-910、887-911、953-977、954-978、977-1001、978-1002、984-1008、985-1009、1035-1059、1038-1062、1095-1119、1096-1120、1097-1121、1098-1122、1105-1129、1119-1143、1129-1153、1130-1154、1144-1168、1199-1223、1200-1224、1201-1225、1203-1227、1210-1234、1211-1235、1212-1236、1216-1240、1218-1242、1233-1257、1240-1264、1268-1292、1281-1305、1299-1323、1301-1325、1302-1326、1305-1329、1307-1331、1308-1332、1311-1335、1347-1371、1384-1408、1385-1409、1386-1410、1392-1416、1393-1417、1394-1418、1396-1420、1402-

1426、1427-1451、1428-1452、1429-1453、1430-1454、1431-1455、1433-1457、1434-1458、1435-1459、1437-1461、1460-1484、1464-1488、1500-1524、1603-1627、1610-1634、1611-1635、1612-1636、1644-1668、1646-1670、1647-1671、1664-1688、1784-1808、1806-1830、1808-1832、1809-1833、1847-1871、1855-1879、1859-1883、1860-1884、1862-1886、1863-1887、1864-1888、2024-2048、2160-2184、2161-2185、2163-2187、2164-2188、2165-2189、2173-2197、2174-2198的核苷酸序列中的任一者相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，並且該反義鏈包含與SEQ ID NO: 2的對應核苷酸序列相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，其中該有義鏈和該反義鏈彼此能夠部分地、基本上或完全互補。

【0011】 在一些實施方案中，提供了用於抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈包含與SEQ ID NO: 1的核苷酸356-376、366-386、403-423、525-545、526-546、559-579、581-601、624-644、630-650、632-652、633-653、634-654、636-656、637-657、638-658、644-664、747-767、766-786、768-788、771-791、773-793、774-794、780-800、781-801、782-802、783-803、784-804、785-805、788-808、790-810、822-842、880-900、881-901、888-908、889-909、955-975、956-976、979-999、980-1000、986-1006、987-1007、1037-1057、1040-1060、1097-1117、1098-1118、1099-1119、1100-1120、1107-1127、1121-1141、1131-1151、1132-1152、1146-1166、1201-1221、1202-1222、1203-1223、1205-1225、1212-

1232、1213-1233、1214-1234、1218-1238、1220-1240、1235-1255、1242-1262、1270-1290、1283-1303、1301-1321、1303-1323、1304-1324、1307-1327、1309-1329、1310-1330、1313-1333、1349-1369、1386-1406、1387-1407、1388-1408、1394-1414、1395-1415、1396-1416、1398-1418、1404-1424、1429-1449、1430-1450、1431-1451、1432-1452、1433-1453、1435-1455、1436-1456、1437-1457、1439-1459、1462-1482、1466-1486、1502-1522、1605-1625、1612-1632、1613-1633、1614-1634、1646-1666、1648-1668、1649-1669、1666-1686、1786-1806、1808-1828、1810-1830、1811-1831、1849-1869、1857-1877、1861-1881、1862-1882、1864-1884、1865-1885、1866-1886、2026-2046、2162-2182、2163-2183、2165-2185、2166-2186、2167-2187、2175-2195、2176-2196、358-376、368-386、405-423、527-545、528-546、561-579、583-601、626-644、632-650、634-652、635-653、636-654、638-656、639-657、640-658、646-664、749-767、768-786、770-788、773-791、775-793、776-794、782-800、783-801、784-802、785-803、786-804、787-805、790-808、792-810、824-842、882-900、883-901、890-908、891-909、957-975、958-976、981-999、982-1000、988-1006、989-1007、1039-1057、1042-1060、1099-1117、1100-1118、1101-1119、1102-1120、1109-1127、1123-1141、1133-1151、1134-1152、1148-1166、1203-1221、1204-1222、1205-1223、1207-1225、1214-1232、1215-1233、1216-1234、1220-1238、1222-1240、1237-1255、1244-1262、1272-1290、1285-1303、1303-1321、1305-1323、1306-1324、1309-1327、1311-1329、1312-1330、1315-1333、1351-1369、1388-

1406,1389-1407、1390-1408、1396-1414、1397-1415、1398-1416、1400-1418、1406-1424、1431-1449、1432-1450、1433-1451、1434-1452、1435-1453、1437-1455、1438-1456、1439-1457、1441-1459、1464-1482、1468-1486、1504-1522、1607-1625、1614-1632、1615-1633、1616-1634、1648-1666、1650-1668、1651-1669、1668-1686、1788-1806、1810-1828、1812-1830、1813-1831、1851-1869、1859-1877、1863-1881、1864-1882、1866-1884、1867-1885、1868-1886、2028-2046、2164-2182、2165-2183、2167-2185、2168-2186、2169-2187、2177-2195、2178-2196、1869-1887的核苷酸序列中的任一者相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，並且該反義鏈包含與SEQ ID NO: 2的對應核苷酸序列相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，其中該有義鏈和該反義鏈彼此能夠部分地、基本上或完全互補。

【0012】 在一些實施方案中，INHBE RNA轉錄本是SEQ ID NO: 1。

【0013】 在一些實施方案中，dsRNA藥劑的反義鏈與SEQ ID NO: 1的任一靶區域至少基本上互補，並且提供在表1至表3中的任一個表中。在一些實施方案中，dsRNA藥劑的反義鏈與SEQ ID NO: 1的任一靶區域完全互補，並且提供在表1至表3中的任一個表中。在一些實施方案中，dsRNA藥劑包含表1至表3中的任一個表中示出的有義鏈序列，其中該有義鏈序列與dsRNA藥劑中的反義鏈序列至少基本上互補。在某些實施方案中，dsRNA藥劑包含表1至表3中的任一個表中示出的有義鏈序列，其中該有義鏈序列與dsRNA藥劑中的反義鏈序列完全互補。在一些實施方案中，dsRNA藥劑包含表1至表3中的任一個表中示出的反義鏈序列。在一些實施

方案中，dsRNA藥劑包含表1至表3中的任一個表中作為雙鏈體序列示出的序列。

【0014】 在一些實施方案中，dsRNA藥劑包含至少一個經修飾的核苷酸。在某些實施方案中，反義鏈的所有或基本上所有核苷酸都是經修飾的核苷酸。在一些實施方案中，經修飾的核苷酸中的至少一者包括：2'-O-甲基核苷酸、2'-氟核苷酸、2'-脫氧核苷酸、2'3'-開環核苷酸模擬物、鎖核苷酸、非鎖核酸核苷酸（UNA）、乙二醇核酸核苷酸（GNA）、2'-F-阿拉伯糖核苷酸、2'-甲氧基乙基核苷酸、無鹼基核苷酸、核糖醇、反向核苷酸、反向無鹼基核苷酸、反向2'-Ome核苷酸、反向2'-脫氧核苷酸、異甘露醇核苷酸、經2'-氨基修飾的核苷酸、經2'-烷基修飾的核苷酸、嗎啉基核苷酸和3'-OMe核苷酸、包含5'-硫代磷酸酯基團的核苷酸、包含5'-磷酸酯模擬物的核苷酸、或與膽甾醇基衍生物或十二烷酸雙癸醯胺基團連接的末端核苷酸、經2'-氨基修飾的核苷酸、包含亞磷醯胺或非天然鹼基的核苷酸。

【0015】 在一些實施方案中，dsRNA藥劑包含在反義鏈的5′-末端處的E-乙烯基膦酸酯核苷酸。

【0016】 在某些實施方案中，dsRNA藥劑包含至少一個硫代磷酸酯核苷間鍵。在某些實施方案中，有義鏈包含至少一個硫代磷酸酯核苷間鍵。在一些實施方案中，反義鏈包含至少一個硫代磷酸酯核苷間鍵。在一些實施方案中，有義鏈包含1、2、3、4、5或6個硫代磷酸酯核苷間鍵。在某些實施方案中，反義鏈包含1、2、3、4、5或6個硫代磷酸酯核苷間鍵。在某些實施方案中，其中有義鏈和反義鏈各自獨立地在 5' 末端包含兩個硫代磷酸酯核苷間鍵。在某些實施方案中，其中有義鏈和反義鏈各自獨立地在 3'

末端包含兩個硫代磷酸酯核苷間鍵。在某些實施方案中，其中有義鏈和反義鏈的每個末端各自獨立地包含兩個硫代磷酸酯核苷間鍵。

【0017】 在一個實施方案中，一個或多個親脂性部分諸如經由接頭或載劑與至少一條鏈上的一個或多個末端位置或內部位置綴合。在一個實施方案中，這些內部位置包括除了距該至少一條鏈的每一端的末端兩個位置之外的所有位置。在另一個實施方案中，這些內部位置包括除了距該至少一條鏈的每一端的末端三個位置之外的所有位置。在一個實施方案中，這些內部位置不包括有義鏈的切割位點區域。在一個實施方案中，這些內部位置不包括反義鏈的切割位點區域。在一個實施方案中，一個或多個親脂性部分與這些內部位置中的一個或多個內部位置綴合，這些內部位置選自從有義鏈的3'端開始計數的有義鏈上的位置4至8和13至18，以及從反義鏈的5'端開始計數的反義鏈上的位置6至10和15至18。在另一個實施方案中，一個或多個親脂性部分與這些內部位置中的一個或多個內部位置綴合，這些內部位置選自從有義鏈的3'-端開始計數的有義鏈上的位置5、6、15、16和17，以及從反義鏈的5'-端開始計數的反義鏈上的位置15至17。在一個實施方案中，雙鏈區中的內部位置不包括有義鏈的切割位點區域。在一個實施方案中，有義鏈的長度為21個核苷酸，反義鏈的長度為21個核苷酸，並且親脂性部分與有義鏈的位置21、位置20、位置15、位置1、位置7、位置6或位置2或從反義鏈的5'端開始計數的反義鏈的位置16綴合。在一個實施方案中，親脂性部分與從有義鏈的3'端開始計數的有義鏈的位置1、位置2、位置7、位置21或位置15綴合。在另一個實施方案中，親脂性部分與從有義鏈的3'端開始計數的有義鏈的位置1、位置2或位置7綴合。在又一個實施方

案中，親脂性部分與從有義鏈的3'端開始計數的有義鏈的位置2或位置7綴合。在一個實施方案中，親脂性部分與從反義鏈的5'端開始計數的反義鏈的位置16綴合。

【0018】 在一個實施方案中，親脂性部分是脂族、脂環族或多脂環族化合物。在一個實施方案中，親脂性部分選自脂質、膽固醇、視黃酸、膽酸、金剛烷乙酸、1-芘丁酸、二氫睾酮、1,3-雙-O(十六烷基)甘油、香葉基氧基己醇、十六烷基甘油、冰片、薄荷醇、1,3-丙二醇、十七烷基、棕櫚酸、肉豆蔻酸、O3-(油醯基)石膽酸、O3-(油醯基)膽烯酸、二甲氧基三苯甲基或吩噁嗪。在一個實施方案中，親脂性部分含有飽和或不飽和的C_4-C_{30}烴鏈，以及選自羥基、胺、羧酸、磺酸根、磷酸根、硫醇、疊氮化物和炔烴的任選取代的官能團。在一個實施方案中，親脂性部分含有飽和或不飽和的C_6-C_{18}烴鏈。在一個實施方案中，親脂性部分含有飽和或不飽和的C_{16}烴鏈。在一個實施方案中，該飽和或不飽和的C_{16}烴鏈與從該鏈的5'-端開始計數的位置15或16綴合。在一個實施方案中，親脂性部分經由替換內部位置或雙鏈區中的一個或多個核苷酸的載劑綴合。在一個實施方案中，該載劑是選自吡咯烷基、吡唑啉基、吡唑烷基、咪唑啉基、咪唑烷基、呱啶基、呱嗪基、[1,3]二氧戊環基、噁唑烷基、異噁唑烷基、嗎啉基、噻唑烷基、異噻唑烷基、喹喔啉基、噠嗪基、四氫呋喃基和十氫萘基的環狀基團；或者是基於絲氨醇骨架或二乙醇胺主鏈的無環部分。在一個實施方案中，親脂性部分經由含有醚、硫醚、脲、碳酸酯、胺、醯胺、馬來醯亞胺-硫醚、二硫化物、磷酸二酯、磺醯胺鍵、點擊反應產物或氨基甲酸酯的接頭與雙鏈iRNA藥劑綴合。在一個實施方案中，親脂性部分與核鹼基、糖部分或核苷間鍵綴合。

在一個實施方案中，親脂性部分經由選自以下的生物接頭進行綴合：DNA、RNA、二硫化物、醯胺、半乳糖胺的官能化單糖或寡糖、葡糖胺、葡萄糖、半乳糖、甘露糖以及它們的組合。

【0019】 在一些實施方案中，有義鏈和反義鏈的所有或基本上所有核苷酸都是經修飾的核苷酸。在一些實施方案中，反義鏈包含15個或更多個經修飾的核苷酸，這些修飾的核苷酸獨立地選自2'-O-甲基核苷酸、2'-氟核苷酸和經UNA修飾的核苷酸，其中少於6個經修飾的核苷酸是2'-氟核苷酸。在一些實施方案中，反義鏈包含3個或5個2'-氟核苷酸，優選地，反義鏈包含5個2'-氟核苷酸。在一些實施方案中，有義鏈包含15個或更多個經修飾的核苷，這些修飾的核苷酸獨立地選自2'-O-甲基核苷酸和2'-氟核苷酸的酸，其中少於4個經修飾的核苷酸是2'-氟核苷酸。在某些實施方案中，有義鏈包含3個2'-氟核苷酸。在一些實施方案中，反義鏈包含15個或更多個經修飾的核苷酸獨立地選自2'-O-甲基核苷酸和2'-氟核苷酸，其中至少14個經修飾的核苷酸是2'-O-甲基核苷酸，並且在從反義鏈的5'端的第一匹配位置開始計數的位置2、5、7、11、12、14、16和/或18處的核苷酸獨立地是2'-氟核苷酸。在一些實施方案中，反義鏈包含至少一個經UNA修飾的核苷酸和5個2'-氟核苷酸。在一些實施方案中，反義鏈包含在位置7處的一個經UNA修飾的核苷酸和在從5'端的第一匹配位置開始計數的位置2、5、12、14和16處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，反義鏈包含在位置7處的一個經UNA修飾的核苷酸和在從5'端的第一匹配位置開始計數的位置2、5、12、14和18處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，反義鏈包含在位置7處的一個經UNA修飾

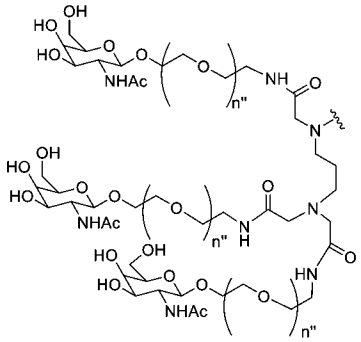
的核苷酸和在從5'端的第一匹配位置開始計數的位置2、5、11、14和16處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，反義鏈包含在從5'端的第一匹配位置開始計數的位置2、7、12、14和16處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，反義鏈包含在從5'端的第一匹配位置開始計數的位置2、7、11、14和16處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，反義鏈包含在從5'端的第一匹配位置開始計數的位置2、5、12、14和16處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，反義鏈包含在從5'端的第一匹配位置開始計數的位置2、5、11、14和16處的5個2'-氟核苷酸，以及其餘的2'-O-甲基核苷酸。在一些實施方案中，有義鏈包含15個或更多個經修飾的核苷酸，獨立地選自2'-O-甲基核苷酸和2'-氟核苷酸的，優選地，其中至少18個經修飾的核苷酸是2'-O-甲基核苷酸，並且在從有義鏈的3'端的第一匹配位置開始計數的位置9、11和/或13處的核苷酸是2'-氟核苷酸。在一些實施方案中，有義鏈包含至少18個為2'-O-甲基核苷酸的經修飾的核苷酸，並且在從有義鏈的3'端的第一匹配位置開始計數的位置8、11和/或13處的核苷酸是2'-氟核苷酸。在一些實施方案中，經修飾的有義鏈是表2至表3中的一個表中示出的經修飾的有義鏈序列。在一些實施方案中，經修飾的反義鏈是表2至表3中的一個表中示出的經修飾的反義鏈序列。

【0020】 在一些實施方案中，dsRNA藥劑包含至少一個經修飾的核苷酸，並且還包含一個或多個靶向基團或連接基團。在一些實施方案中，該一個或多個靶向基團或連接基團與有義鏈綴合。在某些實施方案中，dsRNA藥劑包含與有義鏈的5'-末端綴合的靶向基團。在一些實施方案中，

dsRNA藥劑包含與有義鏈的3'-末端綴合的靶向基團。

【0021】 在一些實施方案中，該靶向基團或連接基團包括N-乙醯基-半乳糖胺（GalNAc）。

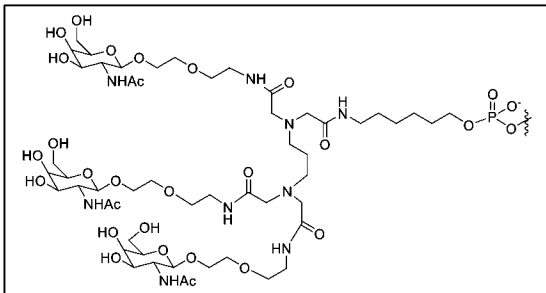
【0022】 在一些實施方案中，該靶向基團具有以下結構：



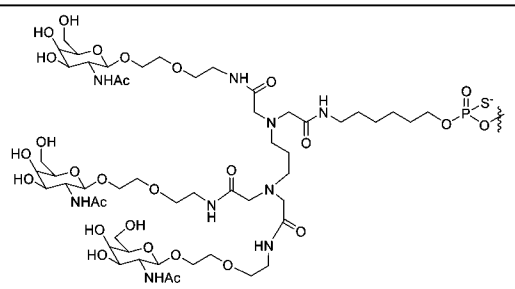
式1；

n''獨立地選自1或2。

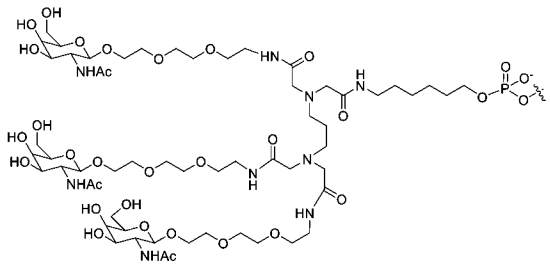
【0023】 在一些實施方案中，該靶向基團具有以下結構：



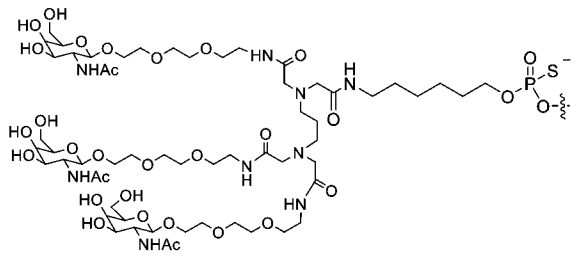
GLO-1



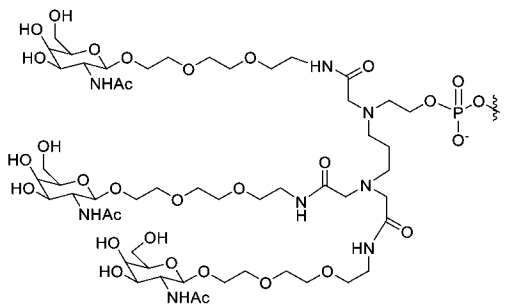
GLS-1*



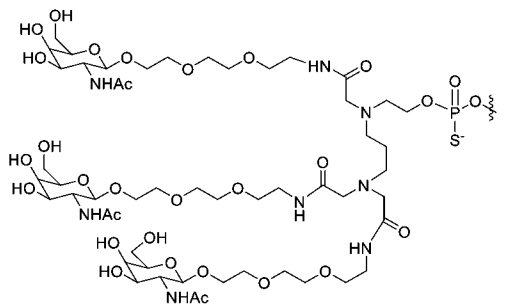
GLO-2



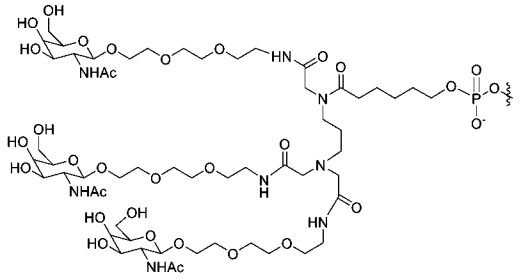
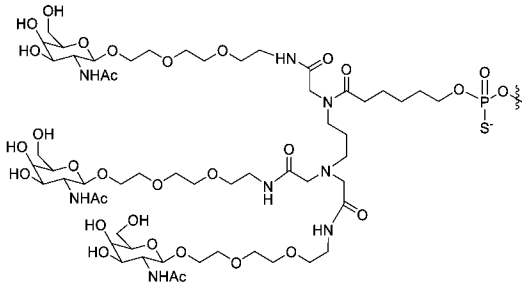
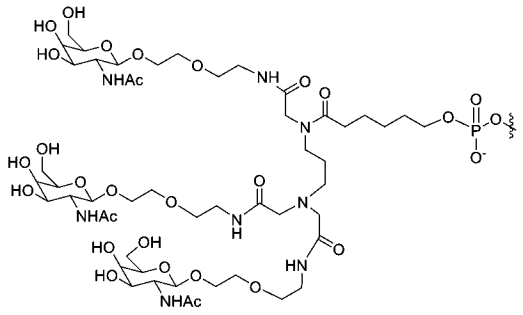
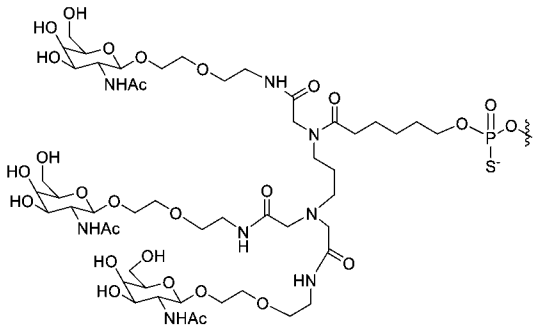
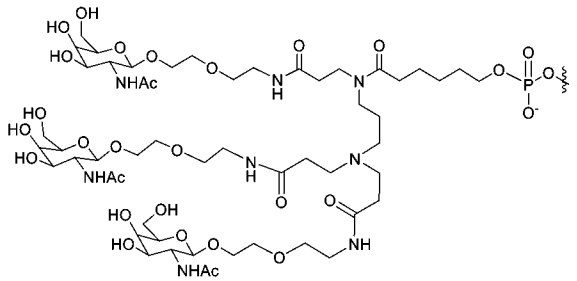
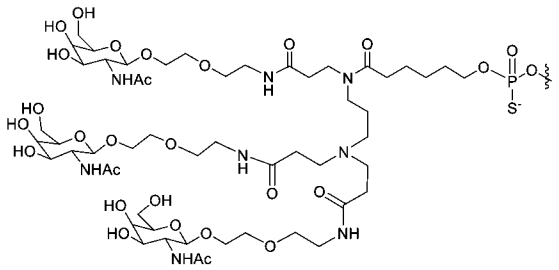
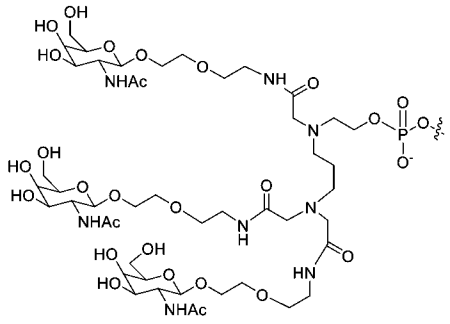
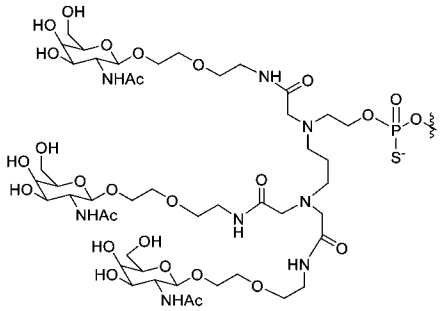
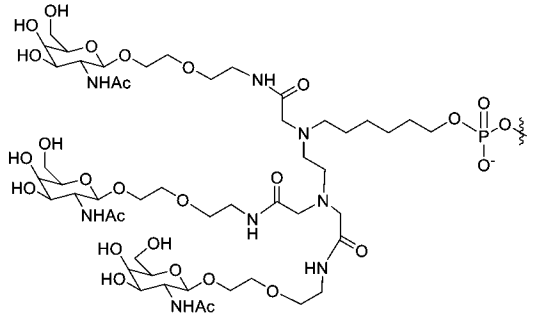
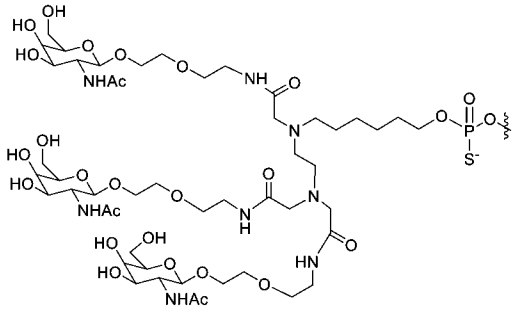
GLS-2*

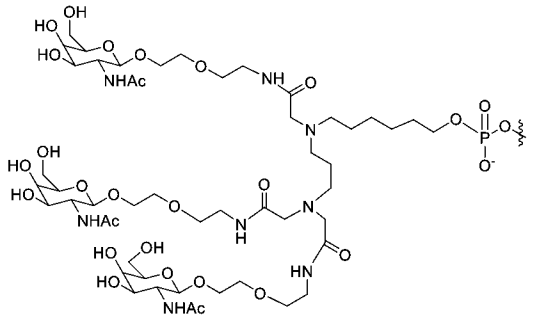


GLO-3

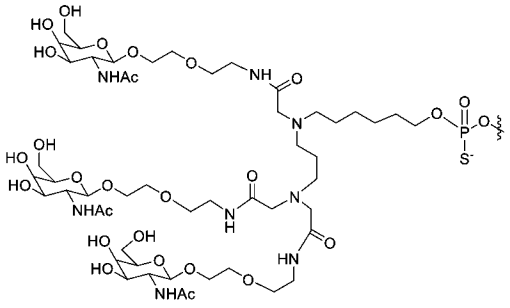


GLS-3*

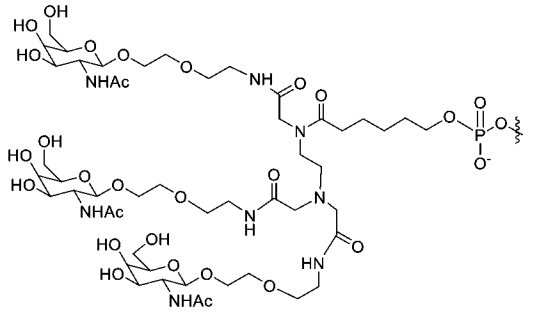
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*
 GLO-6	 GLS-6*
 GLO-7	 GLS-7*
 GLO-8	 GLS-8*



GLO-9



GLS-9*



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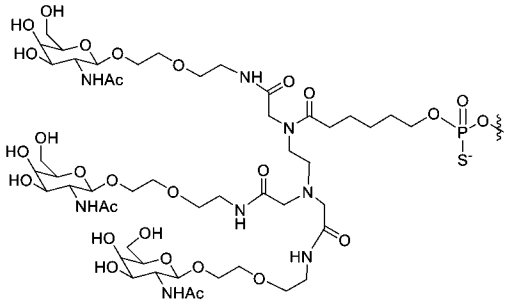

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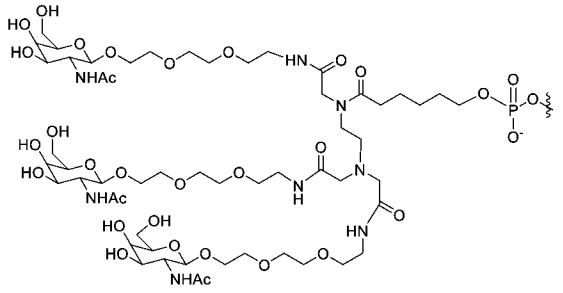

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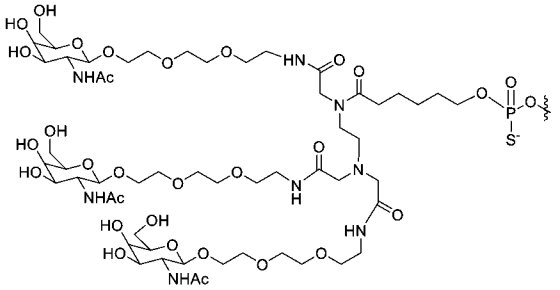

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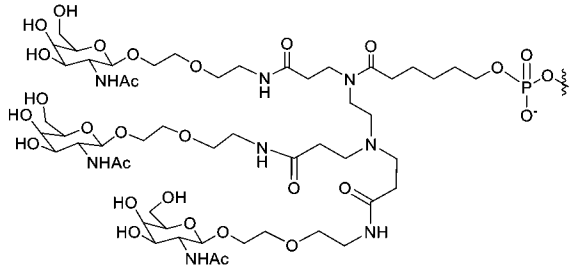

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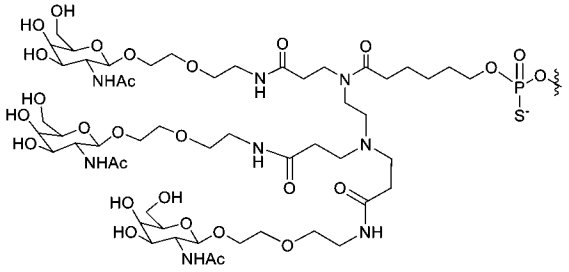

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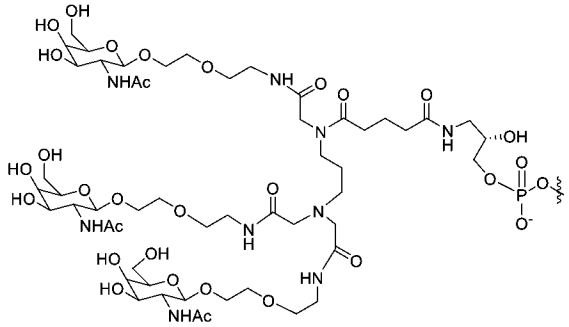
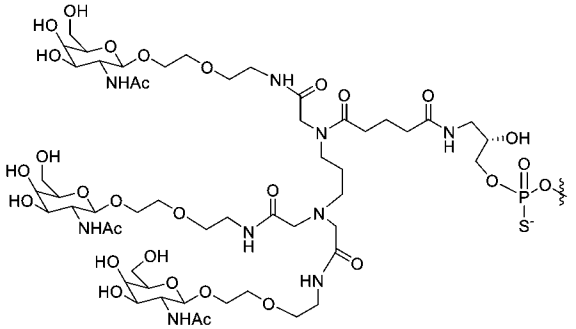
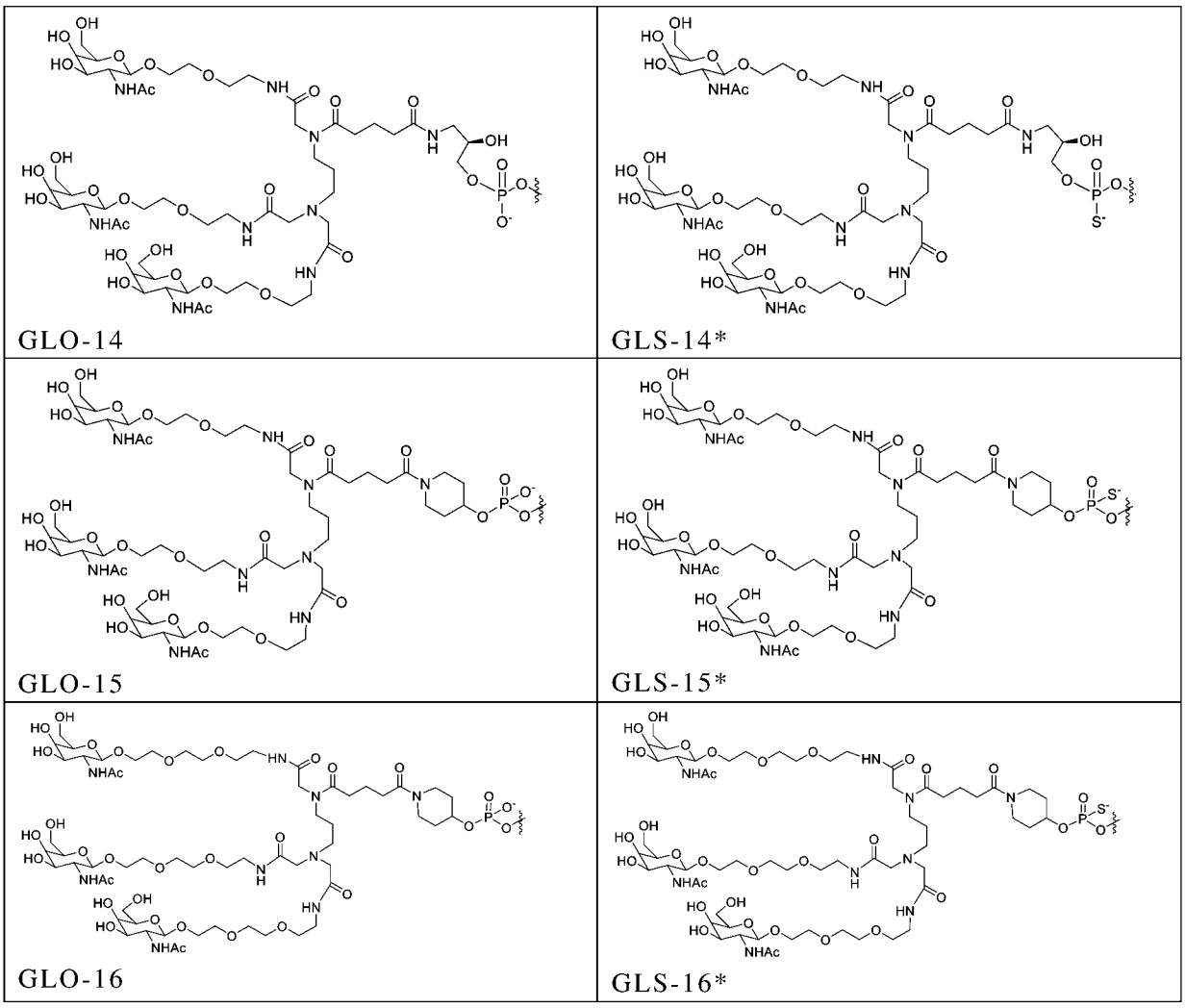


GLO-13



GLS-13*



【0024】 在一些實施方案中，反義鏈包含在3'-末端處的一個反向無鹼基殘基。

【0025】 在某些實施方案中，有義鏈包含在3'或/和5'末端處的一個或兩個反向無鹼基殘基和/或一個或兩個異甘露醇殘基。在某些實施方案中，有義鏈的每一端包含一個反向無鹼基殘基。在某些實施方案中，有義鏈的每一端包含一個異甘露醇殘基。在一些實施方案中，一個或多個反向無鹼基殘基或一個或多個異甘露醇殘基經由硫代磷酸酯鍵與有義鏈的任一端或兩端綴合。在一些實施方案中，靶向基團還經由硫代磷酸酯鍵與有義鏈的任一端綴合。在一些實施方案中，靶向基團還經由硫代磷酸酯鍵與有義鏈

的5'-端綴合。在某些實施方案中，有義鏈的每一端包含在有義鏈的5'末端處的一個反向無鹼基殘基或異甘露醇殘基，其中該反向無鹼基殘基或異甘露醇殘基經由硫代磷酸酯鍵與有義鏈的核苷酸序列的5'末端的相鄰核苷酸連接。在一些實施方案中，一個反向無鹼基殘基通過硫代磷酸酯鍵結合到有義鏈的 3’ 端末端。在一些實施方案中，有義鏈僅包含一個反向無鹼基殘基，其中可選地，其中反向無鹼基殘基通過硫代磷酸酯鍵結合到有義鏈的 3’ 端末端。在某些實施方案中，有義鏈還包含與有義鏈的5'末端處的反向無鹼基殘基或異甘露醇殘基連接的靶向基團，其中該靶向基團經由硫代磷酸酯鍵與相鄰的反向無鹼基殘基或異甘露醇殘基連接，並且任選的靶向基團是N-乙醯基-半乳糖胺（GalNAc）。

【0026】 在一些實施方案中，dsRNA藥劑具有兩個平端。在一些實施方案中，至少一條鏈包含至少1個核苷酸的3'突出端。在一些實施方案中，至少一條鏈包含至少2個核苷酸的3'突出端。

【0027】 在某些實施方案中，dsRNA包括選自AV01605、AV01707、AV01592、AV01593、AV01699、AV01706、AV01710、AV01604、AV01700、AV01705的雙鏈體，並且其中雙鏈體任選地包括靶向配體。在某些實施方案中，dsRNA包括選自AD00964、AD00977、AD01272、AD00926、AD00927、AD00964、AD00968、AD00972、AD00974、AD00977、AD01273、AD00979、AD01274、AD01275、AD00926、AD00927、AD00981、AD01276、AD01277、AD00982和AD00984的雙鏈體。

【0028】 在一些實施方案中，經修飾的有義鏈具有表2至表3中的任一

個表中示出的修飾模式。在一些實施方案中，經修飾的反義鏈具有表2至表3中的任一個表中示出的修飾模式。在一些實施方案中，經修飾的有義鏈是表2至表3中的一個表中示出的經修飾的有義鏈序列。在一些實施方案中，經修飾的反義鏈是表2至表3中的一個表中示出的經修飾的反義鏈序列。

【0029】 在一些實施方案中，提供了一種用於抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈與該反義鏈互補，其中該反義鏈包含與INHBE RNA轉錄本的一部分互補的區域，其中每條鏈的長度為約15至約30個核苷酸，其中該有義鏈包含能夠由式(I)表示的序列：

$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$ (I)；

其中：

每個N'_F表示經2'-氟修飾的核苷酸；每個N'_{N1}和N'_{N2}獨立地表示經修飾或未修飾的核苷酸；每個N'_L獨立地表示經修飾或未修飾的核苷酸但不表示經2'-氟修飾的核苷酸，並且m′和n′各自獨立地為0至7的整數。

【0030】 在一些實施方案中，N'_{N1}和N'_{N2}包括僅一個經2'-氟修飾的核苷酸。

【0031】 在一些實施方案中，N'_{N1}獨立地表示經2'-氟修飾的核苷酸，可選地，N'_{N2}獨立地表示2'-O-甲基修飾的核苷酸。

【0032】 在一些實施方案中，N'_{N2}獨立地表示經2'-氟修飾的核苷酸，可選地，N'_{N1}獨立地表示2'-O-甲基修飾的核苷酸。

【0033】 在一些實施方案中，m'為2並且n'為4，或者m'為2並且n'為2。

在一些實施方案中，m'為1並且n'為4，或者m'為1並且n'為2。在一些實施方案中，m'為0並且n'為4，或者m'為0並且n'為2。在一些實施方案中，每個N'_L獨立地代表 2’-O-甲基核苷酸。

【0034】 在一些實施方案中，dsRNA藥劑包含與有義鏈的5'-末端綴合的靶向基團，優選地，該靶向基團選自上述GLO-1至GLO-16以及GLS-1*至GLS-16*中的任一者，更優選地，該靶向基團是上述GLS-15*。在某些實施方案中，dsRNA藥劑包含與有義鏈的3'-末端綴合的靶向基團。在某些實施方案中，反義鏈包含在3'-末端處的一個反向無鹼基殘基。在某些實施方案中，有義鏈包含在3'或/和5'末端處的一個或兩個反向無鹼基殘基和/或一個或兩個異甘露醇殘基。在某些實施方案中，有義鏈的每個3'末端和5'末端獨立地包含反向無鹼基殘基。在某些實施方案中，有義鏈的每個3'末端和5'末端獨立地包含異甘露醇殘基。在某些實施方案中，有義鏈包含在3'末端和5'末端處的兩個反向無鹼基殘基，並且在3'末端或5'末端處的殘基與優選為上述GLS-15*的靶向基團進一步綴合。在某些實施方案中，有義鏈包含在3'末端和5'末端處的兩個異甘露醇殘基，並且在3'末端或5'末端處的殘基與優選為上述GLS-15*的靶向基團進一步綴合。在某些實施方案中，有義鏈的每一端包含在有義鏈的5'末端處的一個反向無鹼基殘基或異甘露醇殘基，其中該反向無鹼基殘基或異甘露醇殘基經由硫代磷酸酯鍵與有義鏈的核苷酸序列的5'末端的相鄰核苷酸連接。在某些實施方案中，有義鏈還包含與有義鏈的5'末端處的反向無鹼基殘基或異甘露醇殘基連接的靶向基團，其中該靶向基團經由硫代磷酸酯鍵與相鄰的反向無鹼基殘基或異甘露醇殘基連接，並且任選的靶向基團是N-乙醯基-半乳糖胺（GalNAc）。在

一些實施方案中，一個反向無鹼基殘基通過硫代磷酸酯鍵結合到有義鏈的3’端末端。在一些實施方案中，有義鏈僅包含一個反向無鹼基殘基，可選地，其中反向無鹼基殘基通過硫代磷酸酯鍵結合到有義鏈的 3’ 端末端。

【0035】 在一些實施方案中，提供了一種用於抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈與該反義鏈互補，其中該反義鏈包含與INHBE RNA轉錄本互補的區域，其中每條鏈的長度為約18至約30個核苷酸，其中該反義鏈包含能夠由式(II)表示的序列：

$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_{M4}\ N_{M5}\ N_L\ N_L\ N_{M6}\ N_L\ N_{M7}\ N_L\ N_L\ N_F\ N_z\text{-}5'$

(II)；

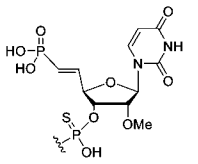
其中：

每個N_F表示經2'-氟修飾的核苷酸；每個N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}和N_{M7}獨立地表示經修飾或未修飾的核苷酸；每個N_L和/或Nz獨立地表示經修飾或未修飾的核苷酸但不表示經2'-氟修飾的核苷酸，並且n為0至7的整數。

【0036】 在一些實施方案中，經修飾的核苷酸是上文定義的經修飾的核苷酸。在一些實施方案中，N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、 N_{M6}、和 N_{M7} 中具有僅三個 2'-氟修飾核苷酸。在一些實施方案中， N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}、和 N_{M7} 獨立地表示 2'-氟修飾核苷酸、2’-O-甲基核苷酸、UNA 修飾核苷酸或包含磷酸鹽模擬物的核苷酸。在一些實施方案中，每個 N_L 和/或 Nz 獨立地表示 2’-O-甲基核苷酸。

【0037】 在一些實施方案中，Nz是包含5'-磷酸酯模擬物的核苷酸。

【0038】 在一些實施方案中，N_Z表示經5'-膦酸酯修飾的核苷酸，優選地，其中所述核苷酸包含乙烯基膦酸酯。

【0039】 在一些實施方案中，Nz是VPu*，其具有結構  。

【0040】 在一些實施方案中，N_{M2}、N_{M3}和N_{M6}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}, N_{M4}, N_{M5} 和N_{M7}獨立地表示2'-O-甲基修飾的核苷酸。

【0041】 在一些實施方案中，N_{M2}、N_{M4}和N_{M6}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}, N_{M3}, N_{M4} 和 N_{M7}獨立地表示2'-O-甲基修飾的核苷酸。

【0042】 在一些實施方案中，N_{M1}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M2}, N_{M4}, N_{M5}和 N_{M6}獨立地表示2'-O-甲基修飾的核苷酸。

【0043】 在一些實施方案中，N_{M2}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}, N_{M4}, N_{M5} 和 N_{M6}獨立地表示2'-O-甲基修飾的核苷酸。

【0044】 在一些實施方案中，N_{M2}、N_{M4}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}、N_{M3}、N_{M5} 和N_{M6} 獨立地表示2'-O-甲基修飾的核苷酸。

【0045】 在一些實施方案中，N_{M2}、N_{M5}和N_{M6}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}、N_{M3}、 N_{M4} 和 N_{M7}獨立地表示2'-O-甲基修飾的核苷酸。

【0046】 在一些實施方案中，N_{M1}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，並且N_{M6}表示經UNA修飾的核苷酸，可選地，N_{M2}, N_{M4} 和N_{M5}獨立地表示2'-O-甲基修飾的核苷酸。

【0047】 在一些實施方案中，N_{M2}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，並且N_{M6}表示經UNA修飾的核苷酸，可選地，N_{M1}, N_{M4} 和N_{M5}獨立地表示2'-O-甲基修飾的核苷酸。

【0048】 在一些實施方案中，N_{M2}、N_{M4}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，並且N_{M6}表示經UNA修飾的核苷酸，可選地，N_{M1}, N_{M3} 和N_{M5}獨立地表示2'-O-甲基修飾的核苷酸。

【0049】 在一些實施方案中，n為1，或者n為2，或者n為3，或者n為5。

【0050】 在一些實施方案中，dsRNA藥劑的反義鏈與SEQ ID NO: 1的任一靶區域至少基本上互補，並且提供在表1至表3中的任一個表中。

【0051】 在一些實施方案中，提供了一種用於抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中該dsRNA藥劑包含有義鏈和反義鏈，其中該有義鏈和該反義鏈形成dsRNA雙鏈體，其中該有義鏈與該反義鏈互補，其中該反義鏈包含與INHBE RNA轉錄本互補的區域，其中該互補區域包含至少15個連續核苷酸，其中該dsRNA雙鏈體包含由式(III)表示的序列：

有義鏈：$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$

反義鏈：$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_{M4}\ N_{M5}\ N_L\ N_L\ N_{M6}\ N_L\ N_{M7}\ N_L\ N_L\ N_F\ N_z\text{-}5'$

(III)；

其中：

每條鏈的長度為約18至約30個核苷酸；

每個N_F和N'_F獨立地表示經2'-氟修飾的核苷酸；N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}、N_{M7}、N'_{N1}和N'_{N2}各自獨立地表示經修飾或未修飾的核苷酸；每個Nz、N_L和N'_L獨立地表示經修飾或未修飾的核苷酸但不表示經2'-氟修飾的核苷酸，並且m'、n'和n各自獨立地為0至7的整數。

【0052】 在一些實施方案中，N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}和N_{M7}具有僅三個經2'-氟修飾的核苷酸，N'_{N1}和N'_{N2}包括僅一個經2'-氟修飾的核苷酸。

【0053】 在一些實施方案中，經修飾的核苷酸是上文定義的經修飾的核苷酸。在一些實施方案中，m'為2並且n'為4，m'為2並且n'為6，或這m'為2並且n'為2。在一些實施方案中，m'為1並且n'為4，或者m'為1並且n'為2。在一些實施方案中，m'為0並且n'為4，或者m'為0並且n'為2。在一些實施方案中，n為1，或者n為2，或者n為3，或者n為5。在一些實施方案中，Nz、N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}、和 N_{M7}獨立地表示 2'-氟修飾核苷酸、2'-O-甲基核苷酸、UNA 修飾核苷酸或包含磷酸鹽模擬物的核苷酸。在一些實施方案中，每個 N_L 和/或N'_L 獨立地表示 2'-O-甲基核苷酸。

【0054】 在一些實施方案中，N'_{N1}獨立地表示經2'-氟修飾的核苷酸，可選地，N'_{N2}獨立地表示2'-O-甲基修飾的核苷酸。

【0055】 在一些實施方案中，N'_{N2}獨立地表示經2'-氟修飾的核苷酸，可選地，N'_{N1} 獨立地表示2'-O-甲基修飾的核苷酸。

【0056】 在一些實施方案中，N_{M2}、N_{M3}和N_{M6}各自獨立地表示經2'-氟

修飾的核苷酸，可選地，N_{M1}、N_{M4}、N_{M5}和N_{M7}獨立地表示2’-O-甲基修飾的核苷酸。

【0057】 在一些實施方案中，N_{M2}、N_{M4}和N_{M6}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}、N_{M3}、N_{M5}和N_{M7}獨立地表示2’-O-甲基修飾的核苷酸。

【0058】 在一些實施方案中，N_{M1}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M2}、N_{M4}、N_{M5}和 N_{M6}獨立地表示2’-O-甲基修飾的核苷酸。

【0059】 在一些實施方案中，N_{M2}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}、N_{M4}、N_{M5}和 N_{M6}獨立地表示2’-O-甲基修飾的核苷酸。

【0060】 在一些實施方案中，N_{M2}、N_{M4}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}, N_{M3}, N_{M5}和 N_{M6}獨立地表示2’-O-甲基修飾的核苷酸。

【0061】 在一些實施方案中，N_{M2}、N_{M5}和N_{M6}各自獨立地表示經2'-氟修飾的核苷酸，可選地，N_{M1}、N_{M3}、N_{M4}和 N_{M7}獨立地表示2’-O-甲基修飾的核苷酸。

【0062】 在一些實施方案中，N_{M1}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，並且N_{M6}表示經UNA修飾的核苷酸，可選地，N_{M2}、N_{M4} 和 N_{M5}獨立地表示2’-O-甲基修飾的核苷酸。

【0063】 在一些實施方案中，N_{M2}、N_{M3}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，並且N_{M6}表示經UNA修飾的核苷酸，可選地，N_{M1}、N_{M4} 和

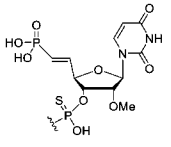
N_{M5}獨立地表示2'-O-甲基修飾的核苷酸。

【0064】 在一些實施方案中，N_{M2}、N_{M4}和N_{M7}各自獨立地表示經2'-氟修飾的核苷酸，並且N_{M6}表示經UNA修飾的核苷酸，可選地，N_{M1}、N_{M3} 和N_{M5}獨立地表示2'-O-甲基修飾的核苷酸。

【0065】 在一些實施方案中，經修飾的核苷酸是上文定義的經修飾的核苷酸。

【0066】 在一些實施方案中，Nz是包含5'-磷酸酯模擬物的核苷酸。

【0067】 在一些實施方案中，N_Z表示經5'-膦酸酯修飾的核苷酸，優選地，其中所述核苷酸包含乙烯基膦酸酯。

【0068】 在一些實施方案中，Nz是VPu*，其具有結構 

。

【0069】 在一些實施方案中，dsRNA藥劑包含與有義鏈的5'-末端綴合的靶向基團，優選地，該靶向基團選自上述GLO-1至GLO-16以及GLS-1*至GLS-16*中的任一者，更優選地，該靶向基團是上述GLS-15*。在某些實施方案中，dsRNA藥劑包含與有義鏈的5'-末端綴合的靶向基團。在某些實施方案中，反義鏈包含在3'-末端處的一個反向無鹼基殘基。在某些實施方案中，有義鏈包含在3'或/和5'末端處的一個或兩個反向無鹼基殘基和/或一個或兩個異甘露醇殘基。在某些實施方案中，有義鏈的每個3'末端和5'末端獨立地包含反向無鹼基殘基。在某些實施方案中，有義鏈的每個3'末端和5'末端獨立地包含異甘露醇殘基。在某些實施方案中，有義鏈包含在3'末端和5'末端處的兩個反向無鹼基殘基，並且在3'末端或5'末端處的殘基與優選為上述GLS-15*的靶向基團進一步綴合。在某些實施方案中，有義鏈包

含在3'末端和5'末端處的兩個異甘露醇殘基，並且在3'末端或5'末端處的殘基與優選為上述GLS-15*的靶向基團進一步綴合。在某些實施方案中，dsRNA藥劑具有兩個平端。在某些實施方案中，至少一條鏈包含至少1個核苷酸的3'突出端。在某些實施方案中，至少一條鏈包含至少2個核苷酸的3'突出端。在一些實施方案中，一個或多個反向無鹼基殘基或一個或多個異甘露醇殘基經由硫代磷酸酯鍵與有義鏈的任一端或兩端綴合。在一些實施方案中，靶向基團還經由硫代磷酸酯鍵與有義鏈的任一端綴合。在一些實施方案中，靶向基團還經由硫代磷酸酯鍵與有義鏈的5'-端綴合。在某些實施方案中，有義鏈的每一端包含在有義鏈的5'末端處的一個反向無鹼基殘基或異甘露醇殘基，其中該反向無鹼基殘基或異甘露醇殘基經由硫代磷酸酯鍵與有義鏈的核苷酸序列的5'末端的相鄰核苷酸連接。在某些實施方案中，有義鏈還包含與有義鏈的5'末端處的反向無鹼基殘基或異甘露醇殘基連接的靶向基團，其中該靶向基團經由硫代磷酸酯鍵與相鄰的反向無鹼基殘基或異甘露醇殘基連接，並且任選的靶向基團是N-乙醯基-半乳糖胺（GalNAc）。在一些實施方案中，一個反向無鹼基殘基通過硫代磷酸酯鍵結合到有義鏈的 3’ 端末端。在一些實施方案中，有義鏈僅包含一個反向無鹼基殘基，可選地，其中反向無鹼基殘基通過硫代磷酸酯鍵結合到有義鏈的 3’ 端末端。在上述dsRNA藥劑的一些實施方案中，與INHBE mRNA轉錄本的一部分互補的區域包含與INHBE mRNA轉錄本的上述任一靶區域的互補物的相差不超過0、1、2或3個核苷酸的至少15、16、17、18或19個連續核苷酸。在某些實施方案中，dsRNA藥劑的反義鏈與SEQ ID NO: 1的任一靶區域至少基本上互補，並且提供在表1至表3中的任一個表中。在上

述dsRNA藥劑的一些實施方案中，INHBE mRNA轉錄本是SEQ ID NO: 1。

【0070】 在一些實施方案中，表1中的任一條有義鏈可以上述式(I)或(III)所示的模式進行進一步修飾。

【0071】 在一些實施方案中，表1中的任一條反義鏈可以上述式(II)或(III)所示的模式進行進一步修飾。

【0072】 在一些實施方案中，表1中的任一個雙鏈體可以上述式(III)所示的模式進行進一步修飾。

【0073】 根據本發明的一個方面，提供了一種組合物，該組合物包含本發明的上述dsRNA藥劑方面的任何實施方案。在某些實施方案中，該組合物還包含藥學上可接受的載劑。在一些實施方案中，該組合物還包含一種或多種另外的治療劑。在某些實施方案中，該組合物被包裝在試劑盒、容器、包裝件、分配器、預填充注射器或小瓶中。在一些實施方案中，該組合物被配製用於皮下施用，被配製用於鞘內施用，或者被配製用於靜脈內（IV）施用。

【0074】 根據本發明的另一個方面，提供了一種細胞，該細胞包含本發明的上述dsRNA藥劑方面的任何實施方案。在一些實施方案中，該細胞是哺乳動物細胞，任選地是人細胞。

【0075】 根據本發明的另一個方面，提供了一種抑制細胞中INHBE基因的表達的方法，該方法包括：(i)製備包含有效量的本發明的上述dsRNA藥劑方面的任何實施方案或本發明的上述組合物的任何實施方案的細胞。在某些實施方案中，該方法還包括：(ii)將所製備的細胞維持足夠長的時間以獲得INHBE基因的mRNA轉錄本的降解，從而抑制細胞中

INHBE基因的表達。在一些實施方案中，該細胞在受試者體內並且通過皮下將dsRNA藥劑施用於該受試者。在一些實施方案中，該細胞在受試者體內並且通過靜脈內施用將dsRNA藥劑施用於該受試者。在一些實施方案中，該細胞在受試者體內並且通過鞘內施用將dsRNA藥劑施用於該受試者。在某些實施方案中，該方法還包括在將dsRNA藥劑施用於受試者後評估對INHBE基因的抑制，其中用於該評估的方式包括：(i)測定受試者的INHBE相關疾病或病症的一種或多種生理特徵，以及(ii)將所測定的生理特徵與該INHBE相關疾病或病症的治療前基線生理特徵和/或該INHBE相關疾病或病症的對照生理特徵進行比較，其中該比較表明對受試者中的INHBE基因表達的抑制存在或不存在中的一者或多者。在一些實施方案中，該生理特徵是以下中的一者或多者：INHBE mRNA水平和INHBE蛋白水平，或者是代謝障礙的一種或多種症狀。

【0076】 根據本發明的另一個方面，提供了一種抑制受試者中的INHBE基因的表達的方法，該方法包括向該受試者施用有效量的本發明的上述dsRNA藥劑方面的實施方案或本發明的上述組合物的實施方案。在一些實施方案中，通過皮下將dsRNA藥劑施用於受試者。在某些實施方案中，通過靜脈內施用將dsRNA藥劑施用於受試者。在一些實施方案中，通過鞘內施用將dsRNA藥劑施用於受試者。在一些實施方案中，該方法還包括在施用dsRNA藥劑後評估對INHBE基因的抑制，其中用於該評估的方式包括：(i)測定受試者的INHBE相關疾病或病症的一種或多種生理特徵，以及(ii)將所測定的生理特徵與該INHBE相關疾病或病症的治療前基線生理特徵和/或該INHBE相關疾病或病症的對照生理特徵進行比較，其中該比較表

明對受試者中的INHBE基因表達的抑制存在或不存在中的一者或多者。在一些實施方案中，INHBE基因的表達可基於與INHBE基因表達相關的任何變量的水平或水平變化（諸如INHBE mRNA水平、INHBE蛋白水平）來評估。INHBE表達的降低還可通過測量INHBE生物活性的降低或受試者的根據體重指數調整的腰臀比的降低來間接評估。鑒定與更有利的脂肪分佈（諸如較低的WHR，特別是當針對BMI進行校正時）相關的遺傳變體，可作為一種鑒定在治療這些心臟代謝疾病中可帶來獲益的機制的途徑。

【0077】 根據本發明的另一個方面，提供了一種治療與INHBE蛋白的存在相關的疾病或病症的方法，該方法包括：向受試者施用有效量的本發明的任何上述dsRNA藥劑方面的實施方案或本發明的任何上述組合物的實施方案，以抑制INHBE基因表達。在一個實施方案中，該障礙是與INHBE相關的障礙。在一個實施方案中，該障礙與INHBE基因編碼的蛋白質的異常有關。在某些實施方案中，“INHBE相關疾病”包括代謝障礙，諸如2型糖尿病、肥胖症（特別是腹部肥胖症）、脂肪代謝障礙（諸如無法在區域性脂肪庫中沉積脂肪（部分脂肪代謝障礙）或者無法在全身沉積脂肪（脂肪萎縮））、肝臟脂肪沉積或脂肪肝病及其併發症（諸如，例如肝硬化、纖維化或肝臟炎症）、高脂血症或血脂異常（低密度脂蛋白膽固醇（LDL-C）、甘油三酯、極低密度脂蛋白膽固醇（VLDL-C）、載脂蛋白B或其他脂質成分的循環水平高或改變）、肝酶水平或其他肝損傷標誌物（諸如，例如ALT和/或AST）較高或升高或改變、非酒精性脂肪性肝炎（NASH）、胰島素抵抗或者在空腹或代謝挑戰期間的胰島素水平較高或改變、其他類型的肝臟炎症和/或甘油三酯水平升高，和/或心血管疾病，諸如心肌病、心

力衰竭，以及高血壓和/或高血壓症、血糖或葡萄糖較高或高血糖症、代謝症候群、冠狀動脈疾病和其他冠狀動脈粥樣硬化病症，以及上述病症中的每一者的併發症。

【0078】 在一些實施方案中，該方法還包括：向受試者施用另外的治療方案。在一些實施方案中，該另外的治療方案包括治療INHBE相關疾病或病症。在某些實施方案中，該另外的治療方案包括：向受試者施用一種或多種本發明的INHBE反義多核苷酸，向受試者施用非INHBE dsRNA治療劑，以及對受試者的行為矯正。在一些實施方案中，該另外的治療劑選自寡核苷酸、小分子、單克隆抗體、多克隆抗體和肽。在一些實施方案中，該代謝障礙是2型糖尿病，該另外的治療劑選自二甲雙胍、胰島素、格列本脲、格列吡嗪、格列美脲、瑞格列奈、那格列奈、噻唑烷二酮、羅格列酮、吡格列酮、西他列汀、沙格列汀、利拉利汀、艾塞那肽、利拉魯肽、司美格魯肽、卡格列淨、達格列淨和恩格列淨，或它們的任何組合。在一些實施方案中，該代謝障礙是肥胖症，該另外的治療劑選自芬特明、托吡酯、安非他酮、納曲酮和利拉魯肽，或它們的任何組合。在一些實施方案中，該代謝障礙是甘油三酯升高，該另外的治療劑選自瑞舒伐他汀、辛伐他汀、阿托伐他汀、非諾貝特、吉非貝齊、非諾貝酸、尼克酸和ω-3脂肪酸，或它們的任何組合。在一些實施方案中，該代謝障礙是脂肪代謝障礙，該另外的治療劑選自替莫瑞林、二甲雙胍、聚-L-乳酸、羥基磷灰石鈣、聚甲基丙烯酸甲酯、牛膠原蛋白、人膠原蛋白、矽酮和透明質酸，或它們的任何組合。在一些實施方案中，該代謝障礙是肝臟炎症，該另外的治療劑選自肝炎治療劑或肝炎疫苗。該代謝障礙是高膽固醇血症，該另外的治療劑選自：

阿托伐他汀、氟伐他汀、洛伐他汀、匹伐他汀、普伐他汀、瑞舒伐他汀鈣、辛伐他汀、考來烯胺、考來維侖和考來替泊、阿利西尤單抗、依洛尤單抗、煙酸、速釋煙酸、非諾貝特、吉非貝齊和貝培多酸，或它們的任何組合。該代謝障礙是肝酶升高，該另外的治療劑選自咖啡、葉酸、鉀、維生素B6、他汀類和纖維素，或它們的任何組合。在一些實施方案中，該代謝障礙是非酒精性脂肪性肝炎（NASH），該另外的治療劑選自奧貝膽酸、司隆色替、埃拉菲布拉諾、西尼昔洛韋、GR_MD_02、MGL_3196、IMM124E、二十烷醯胺基膽烷酸、GS0976、恩利卡生、Volixibat、NGM282、GS9674、卓匹非索、MN_001、LMB763、Bl_1467335、MSDC_0602、PF_05221304、DF102、沙羅格列紮、BMS986036、拉尼蘭諾、司美格魯肽、硝唑尼特、GRI_0621、EYP001、VK2809、納美芬、LIK066、MT_3995、依洛昔巴、納莫德森、福雷蘆單抗、SAR425899、索格列淨、EDP_305、艾考布特、吉卡賓、TERN_101、KBP_042、PF_06865571、DUR928、PF_06835919、NGM313、BMS_986171、那馬西佐單抗、CER_209、ND_L02_s0201、RTU_1096、DRX_065、IONIS_DGAT2Rx、INT_767、NC_001、司拉德帕、PXL770、TERN_201、NV556、AZD2693、SP_1373、VK0214、肝源性幹細胞、TGFTX4、RLBN1127、GKT_137831、RYI_018、CB4209-CB4211和JH_0920。在一些實施方案中，心血管疾病是高血壓，該另外的治療劑選自氯噻酮、氯噻嗪、氫氯噻嗪、吲達帕胺、美托拉宗、醋丁洛爾、阿替洛爾、倍他洛爾、富馬酸比索洛爾、鹽酸卡替洛爾、酒石酸美托洛爾、琥珀酸美托洛爾、納多洛爾、鹽酸貝那普利、卡托普利、馬來酸依那普利、福辛普利鈉、賴諾普利、莫昔普利、培哚普利、鹽酸喹那普利、雷米普利、

群多普利、坎地沙坦、甲磺酸依普沙坦、厄貝沙坦、洛沙坦鉀、替米沙坦、纈沙坦、苯磺酸氨氯地平、苄普地爾、鹽酸地爾硫卓、非洛地平、伊拉地平、尼卡地平、硝苯地平、尼索地平、鹽酸維拉帕米、甲磺酸多沙唑嗪、鹽酸哌唑嗪、鹽酸特拉唑嗪、甲基多巴、卡維地洛、鹽酸拉貝洛爾、α甲基多巴、鹽酸可樂定、乙酸胍那苄、鹽酸胍法辛、胍那決爾、單硫酸胍乙啶、利血平、鹽酸肼屈嗪和米諾地爾，或它們的任何組合。在一些實施方案中，心血管疾病是心肌病，該另外的治療劑選自ACE抑制劑、血管緊張素II受體阻斷劑、β阻斷劑、鈣通道阻斷劑、地高辛、抗心律失常藥、醛固酮阻斷劑、利尿劑、抗凝血劑、血液稀釋劑和皮質類固醇。在一些實施方案中，心血管疾病是心力衰竭，該另外的治療劑選自ACE抑制劑、血管緊張素-2受體阻斷劑、β阻斷劑、鹽皮質激素受體拮抗劑、利尿劑、伊伐佈雷定、沙庫巴曲纈沙坦、硝酸鹽肼屈嗪和地高辛。

【0079】 在一些實施方案中，通過皮下將dsRNA藥劑施用於受試者。在某些實施方案中，通過靜脈內施用將dsRNA藥劑施用於受試者。在一些實施方案中，通過鞘內將dsRNA藥劑施用於受試者。在一些實施方案中，該方法還包括測定所施用的雙鏈核糖核酸（dsRNA）藥劑對受試者的功效。

【0080】 在一些實施方案中，測定該治療對受試者的功效的方式包括：(i)測定受試者的INHBE相關疾病或病症的一種或多種生理特徵，以及(ii)將所測定的生理特徵與該INHBE相關疾病或病症的治療前基線生理特徵進行比較，其中該比較表明向受試者施用的雙鏈核糖核酸（dsRNA）藥劑的存在、不存在和功效水平中的一者或多者。

【0081】 在一些實施方案中，INHBE基因的表達可基於與INHBE基

因表達相關的任何變量的水平或水平變化（諸如受試者的INHBE mRNA水平、INHBE蛋白水平，或者受試者的根據體重指數調整的腰臀比）來評估。

【0082】 根據本發明的另一個方面，提供了一種與受試者的INHBE蛋白的基線治療前水平相比降低該受試者的INHBE蛋白水平的方法，該方法包括向該受試者施用有效量的本發明的任何上述dsRNA藥劑的實施方案或本發明的任何上述組合物的實施方案，以降低INHBE基因表達的水平。在一些實施方案中，通過皮下將dsRNA藥劑施用於受試者，或者通過靜脈內施用將其施用於受試者。在一些實施方案中，通過鞘內將dsRNA藥劑施用於受試者。在又一個實施方案中，通過腦池內將dsRNA藥劑施用於受試者。非限制性的示例性腦池內施用包括通過枕骨下穿刺注射到枕大池（小腦延髓池）中。

【0083】 根據本發明的另一個方面，提供了一種與受試者的INHBE相關疾病或病症的治療前基線生理特徵相比改變該受試者的該INHBE相關疾病或病症的生理特徵的方法，該方法包括向該受試者施用有效量的本發明的任何上述dsRNA藥劑的實施方案或本發明的任何上述組合物的實施方案，以改變該受試者的該INHBE相關疾病或病症的生理特徵。在一些實施方案中，通過皮下將dsRNA藥劑施用於受試者，或者通過靜脈內施用將其施用於受試者。在一些實施方案中，通過鞘內將dsRNA藥劑施用於受試者。在又一個實施方案中，通過腦池內將dsRNA藥劑施用於受試者。非限制性的示例性腦池內施用包括通過枕骨下穿刺注射到枕大池（小腦延髓池）中。在某些實施方案中，生理特徵和症狀是以下中的一者或多者：受試者的INHBE mRNA水平、INHBE蛋白水平，或受試者的根據體重指數調

整的腰臀比。

【0084】 根據本發明的另一個方面，提供了在治療與INHBE蛋白的存在相關的疾病或病症的方法中使用的上述dsRNA藥劑。在一些實施方案中，該疾病或病症是以下中的一者或多者：2型糖尿病、肥胖症（特別是腹部肥胖症）、脂肪代謝障礙（諸如無法在區域性脂肪庫中沉積脂肪（部分脂肪代謝障礙）或者無法在全身沉積脂肪（脂肪萎縮））、肝臟脂肪沉積或脂肪肝病及其併發症（諸如，例如肝硬化、纖維化或肝臟炎症）、高脂血症或血脂異常（低密度脂蛋白膽固醇（LDL-C）、甘油三酯、極低密度脂蛋白膽固醇（VLDL-C）、載脂蛋白B或其他脂質成分的循環水平高或改變）、肝酶水平或其他肝損傷標誌物（諸如，例如ALT和/或AST）較高或升高或改變、非酒精性脂肪性肝炎（NASH）、胰島素抵抗或者在空腹或代謝挑戰期間的胰島素水平較高或改變、其他類型的肝臟炎症和/或甘油三酯水平升高，和/或心血管疾病，諸如心肌病、心力衰竭，以及高血壓和/或高血壓症、血糖或葡萄糖較高或高血糖症、代謝症候群、冠狀動脈疾病和其他冠狀動脈粥樣硬化病症，以及上述病症中的每一者的併發症。

【0085】 根據本發明的另一個方面，提供了一種用於抑制INHBE蛋白的表達的反義多核苷酸藥劑，該藥劑包含10至30個連續核苷酸，其中這些連續核苷酸中的至少一個核苷酸是經修飾的核苷酸，並且其中該藥劑的核苷酸序列在其整個長度上與SEQ ID NO: 1的核苷酸序列的等同區域約80%互補。在一些實施方案中，該等同區域是SEQ ID NO: 1的任一靶區域，並且該補序列是提供在表1至表3中的一個表中的互補序列。在某些實施方案中，該反義多核苷酸藥劑包含提供在表1至表3中的一個表中的反義序列

中的一個反義序列。

【0086】 根據本發明的另一個方面，提供了一種組合物，該組合物包含任何上述反義多核苷酸藥劑的實施方案。在一些實施方案中，該組合物還包含藥學上可接受的載劑。在一些實施方案中，該組合物還包含用於治療INHBE相關疾病或病症的一種或多種另外的治療劑。在某些實施方案中，該組合物被包裝在試劑盒、容器、包裝件、分配器、預填充注射器或小瓶中。在某些實施方案中，該組合物被配製用於皮下、眼內、玻璃體內、鞘內或靜脈內施用。

【0087】 根據本發明的另一個方面，提供了一種細胞，該細胞包含任何上述反義多核苷酸藥劑的實施方案。在一些實施方案中，該細胞是哺乳動物細胞，任選地是人細胞。

【0088】 根據本發明的另一個方面，提供了一種抑制細胞中INHBE基因的表達的方法，該方法包括：(i)製備包含有效量的任何上述反義多核苷酸藥劑的實施方案的細胞。在一些實施方案中，該方法還包括(ii)將(i)中製備的細胞維持足夠長的時間以獲得INHBE基因的mRNA轉錄本的降解，從而抑制細胞中INHBE基因的表達。

【0089】 根據本發明的另一個方面，提供了一種抑制受試者中的INHBE基因的表達的方法，該方法包括向受試者施用有效量的任何上述反義多核苷酸藥劑的實施方案。

【0090】 根據本發明的另一個方面，一種治療與INHBE蛋白的存在相關的疾病或病症的方法，該方法包括向受試者施用有效量的本發明的任何上述反義多核苷酸藥劑的實施方案或任何上述組合物的實施方案，以抑

制INHBE基因表達。在某些實施方案中，該疾病或病症是以下中的一者或多者：2型糖尿病、肥胖症（特別是腹部肥胖症）、脂肪代謝障礙（諸如無法在區域性脂肪庫中沉積脂肪（部分脂肪代謝障礙）或者無法在全身沉積脂肪（脂肪萎縮））、肝臟脂肪沉積或脂肪肝病及其併發症（諸如，例如肝硬化、纖維化或肝臟炎症）、高脂血症或血脂異常（低密度脂蛋白膽固醇（LDL-C）、甘油三酯、極低密度脂蛋白膽固醇（VLDL-C）、載脂蛋白B或其他脂質成分的循環水平高或改變）、肝酶水平或其他肝損傷標誌物（諸如，例如ALT和/或AST）較高或升高或改變、非酒精性脂肪性肝炎（NASH）、胰島素抵抗或者在空腹或代謝挑戰期間的胰島素水平較高或改變、其他類型的肝臟炎症和/或甘油三酯水平升高，和/或心血管疾病，諸如心肌病、心力衰竭，以及高血壓和/或高血壓症、血糖或葡萄糖較高或高血糖症、代謝症候群、冠狀動脈疾病和其他冠狀動脈粥樣硬化病症，以及上述病症中的每一者的併發症。

【0091】 根據本發明的另一個方面，提供了一種與受試者的INHBE蛋白的基線治療前水平相比降低該受試者的INHBE蛋白水平的方法，該方法包括向該受試者施用有效量的本發明的任何上述反義多核苷酸藥劑的實施方案或任何上述組合物的實施方案，以降低INHBE基因表達的水平。在某些實施方案中，通過皮下或靜脈內施用將反義多核苷酸藥劑施用於受試者。在一些實施方案中，通過鞘內將反義多核苷酸藥劑施用於受試者。在又一個實施方案中，通過腦池內將反義多核苷酸藥劑施用於受試者。非限制性的示例性腦池內施用包括通過枕骨下穿刺注射到枕大池（小腦延髓池）中。

【0092】 根據本發明的另一個方面，提供了一種用於抑制INHBE基因的表達的反義多核苷酸藥劑，該藥劑包含10至30個連續核苷酸，其中這些連續核苷酸中的至少一個核苷酸是經修飾的核苷酸，並且其中該藥劑的核苷酸序列在其整個長度上與SEQ ID NO: 1的核苷酸序列的等同區域約80%或約85%互補。

【0093】 根據本發明的另一個方面，提供了一種與受試者的INHBE相關疾病或病症的治療前基線生理特徵相比改變該受試者的該INHBE相關疾病或病症的生理特徵的方法，該方法包括向該受試者施用有效量的本發明的任何上述反義多核苷酸藥劑的實施方案或任何上述組合物的實施方案，以改變該受試者的該INHBE相關疾病或病症的生理特徵。在一些實施方案中，通過鞘內或靜脈內施用將反義多核苷酸藥劑施用於受試者。在一些實施方案中，通過鞘內將反義多核苷酸藥劑施用於受試者。在又一個實施方案中，通過腦池內將反義多核苷酸藥劑施用於受試者。非限制性的示例性腦池內施用包括通過枕骨下穿刺注射到枕大池（小腦延髓池）中。在某些實施方案中，生理特徵和症狀是以下中的一者或多者：受試者的INHBE mRNA水平、INHBE蛋白水平，或運動、認知和行為損傷的不同進展，或包括受試者的根據體重指數調整的腰臀比的症狀和標誌。

序列的簡要描述

【0094】 SEQ ID NO: 1和SEQ ID NO: 2（反向互補物）是智人INHBE mRNA [NCBI參考序列：NM_031479.5]。

【0095】 SEQ ID NO: 3和SEQ ID NO: 4（反向互補物）是小家鼠（家鼠）INHBE mRNA [NCBI參考序列：NM_008382.3]。

【0096】 SEQ ID NO: 5和SEQ ID NO: 6（反向互補物）是褐家鼠（挪威大鼠）INHBE mRNA [NCBI參考序列：NM_031815.3]。

【0097】 SEQ ID NO: 7和SEQ ID NO: 8（反向互補物）是預測的獼猴（恆河猴）INHBE mRNA [NCBI參考序列：XM_001115958.3]。

【0098】 SEQ ID NO: 9-260, 851-1036示於表1中並且都是有義鏈序列。

【0099】 SEQ ID NO: 261-512, 1037-1222示於表1中並且都是反義鏈序列。

【0100】 SEQ ID NO: 513-764, 1223-1824示於表2中並且都具有化學修飾。

【0101】 SEQ ID NO: 765-850, 1825-1934示於表3中。遞送分子在每條有義鏈的3'端或5'端處被表示為“GLX-_”。

【實施方式】

【0102】 本發明部分地包括RNAi藥劑，例如但不限於雙鏈（ds）RNAi藥劑，其能夠抑制抑制素亞基βE（INHBE）基因表達。本發明還部分地包括包含INHBE RNAi藥劑的組合物以及使用這些組合物的方法。本文公開的INHBE RNAi藥劑可與遞送化合物連接以用於遞送至細胞，包括肝細胞。本發明的藥物組合物可包含至少一種dsRNA INHBE藥劑和遞送化合物。在本發明的組合物和方法的一些實施方案中，遞送化合物是含GalNAc的遞送化合物。遞送至細胞的INHBE RNAi藥劑能夠抑制INHBE基因表達，從而降低細胞中該基因的INHBE蛋白產物的活性。本發明的dsRNAi藥劑可用

於治療INHBE相關疾病和病症。

【0103】在本發明的一些實施方案中，降低細胞或受試者中的INHBE表達分別治療與細胞或受試者中的INHBE表達相關的疾病或病症。可通過降低INHBE活性治療的疾病和病症的非限制性示例是：緩解或改善與不期望的或過度的INHBE表達、代謝障礙或者受試者的根據體重指數調整的腰臀比相關的一種或多種症狀。“治療”也可以意指與未接受治療時的預期生存期相比延長生存期。

【0104】本文所用的“任選地”或“可選地”是指後面描述的事件或環境可以但不必發生，包括該事件或環境發生或未發生的情況。

【0105】如本文所用，“G”、“C”、“A”和“U”各自通常分別代表含有鳥嘌呤、胞嘧啶、腺嘌呤和尿嘧啶作為鹼基的核苷酸。然而，應當理解，術語“核糖核苷酸”或“核苷酸”也可以是指經修飾的核苷酸，如下文進一步詳述，或替代替換部分。技術人員應當理解，鳥嘌呤、胞嘧啶、腺嘌呤和尿嘧啶可被其他部分替換，而基本上不改變包含帶有此類替換部分的核苷酸的寡核苷酸的鹼基配對特性。例如，非限制性地，包含肌苷作為其鹼基的核苷酸可與含有腺嘌呤、胞嘧啶或尿嘧啶的核苷酸進行鹼基配對。因此，本發明的核苷酸序列中含有尿嘧啶、鳥嘌呤或腺嘌呤的核苷酸可被含有例如肌苷的核苷酸替換。包含此類替換部分的序列是本發明的實施方案。

【0106】如本文所用，“抑制素亞基βE”可與術語“INHBE”互換使用，是指屬於轉化生長因子（TGF）家族的生長因子，也稱為“抑制素βE鏈”、“活化素βE”、“抑制素βE亞基”、“抑制素βE”，並且“MGC4638”是指編碼稱為抑制素亞基βE蛋白（INHBE）的蛋白質的基因，該蛋白質來自任何脊椎

動物或哺乳動物，包括但不限於人、牛、雞、齧齒類動物、小鼠、大鼠、豬、羊、靈長類動物、猴和豚鼠，除非另有說明。該術語也指天然INHBE的保持天然INHBE的至少一種體內或體外活性的片段和變體。人INHBE基因的參考序列的氨基酸和完整編碼序列可參見例如GenBank參考序列登錄號NM_031479.5（智人INHBE mRNA，SEQ ID NO: 1，反向互補物，SEQ ID NO: 2）；GenBank登錄號NM_008382.3（小家鼠（家鼠）INHBE mRNA，SEQ ID NO: 3，反向互補物，SEQ ID NO: 4）；GenBank登錄號NM_031815.3（褐家鼠（挪威大鼠）INHBE mRNA，SEQ ID NO: 5；反向互補物，SEQ ID NO: 6）；預測的GenBank登錄號XM_001115958.3（獼猴（恆河猴）INHBE SEQ ID NO: 7；反向互補物；SEQ ID NO: 8）；INHBE mRNA序列的其他示例可容易地使用公眾可獲得的數據庫獲得，例如GenBank、UniProt、Ensembl和OMIM。

【0107】 下文描述了如何製備和使用包含INHBE單鏈（ssRNA）和dsRNA藥劑的組合物以抑制INHBE基因表達，以及用於治療由INHBE基因表達引起或調節的疾病和病症的組合物和方法。術語“RNAi”也是本領域已知的，並且可稱為“siRNA”。

【0108】 如本文所用，術語“RNAi”是指包含RNA並經由RNA誘導的沉默複合物（RISC）途徑來介導RNA轉錄本的靶向切割的藥劑。如本領域所知，RNAi靶區域是指在基因轉錄期間形成的mRNA分子的核苷酸序列的連續部分，包括作為初級轉錄產物的RNA加工產物的信使RNA（mRNA）。該序列的靶部分至少足夠長，以便在該部分或其附近用作RNAi指導的切割的底物。靶序列可為8至30個核苷酸長（包括端值）、10至30個核苷酸長（包

括端值）、12至25個核苷酸長（包括端值）、15至23個核苷酸長（包括端值）、16至23個核苷酸長（包括端值）、或18至23個核苷酸長（包括端值），包括在每個所述範圍內的所有更短的長度。在本發明的一些實施方案中，靶序列為9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25或26個核苷酸長。在某些實施方案中，靶序列的長度為9至26個核苷酸之間（包括端值），包括其間的所有子範圍和整數。例如，儘管並非旨在限制，但在本發明的某些實施方案中，靶序列為8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30個核苷酸長，其中該序列與INHBE基因的RNA轉錄本的至少一部分完全或至少基本上互補。本發明的一些方面包括藥物組合物，這些藥物組合物包含一種或多種INHBE dsRNA藥劑和藥學上可接受的載劑。在本發明的某些實施方案中，本文所述的INHBE RNAi抑制INHBE蛋白的表達。

【0109】 如本文所用，“dsRNA藥劑”意指含有RNA或RNA樣（例如，經化學修飾的RNA）寡核苷酸分子的組合物，該組合物能夠以序列特異性方式降解或抑制靶mRNA的信使RNA（mRNA）轉錄本的翻譯。儘管不希望受到特定理論的限制，但本發明的dsRNA藥劑可通過RNA干擾機制（即，通過與哺乳動物細胞的RNA干擾途徑機制（RNA誘導的沉默複合物或RISC）進行相互作用來誘導RNA干擾）或者通過任何替代機制或途徑起作用。使植物、無脊椎動物和脊椎動物細胞中的基因沉默的方法是本領域眾所周知的[參見，例如，（Sharp等人，Genes Dev.2001, 15:485；Bernstein等人，(2001) Nature 409:363；Nykanen等人，(2001) Cell 107:309；以及Elbashir等人，(2001) Genes Dev.15:188），這些文獻中的每一篇的公開內

容以引用方式全文併入本文]。本領域已知的基因沉默方法可與本文提供的公開內容聯合使用，以抑制INHBE的表達。

【0110】 本文公開的dsRNA藥劑由有義鏈和反義鏈組成，並且包含但不限於：短干擾RNA（siRNA）、RNAi藥劑、微小RNA（miRNA）、短髮夾RNA（shRNA）和dicer底物。本文所述的dsRNA藥劑的反義鏈與所靶向的mRNA至少部分地互補。本領域應當理解，不同長度的dsRNA雙鏈體結構可用於抑制靶基因表達。例如，已知具有19、20、21、22和23個鹼基對的雙鏈體結構的dsRNA可有效誘導RNA干擾（Elbashir等人，EMBO 2001, 20:6877-6888）。本領域還已知的是，更短或更長的RNA雙鏈體結構也會有效誘導RNA干擾。在一些實施方案中，有義鏈和反義鏈可具有相同長度或不同長度。在一些實施方案中，每條鏈的長度不超過40個核苷酸。在一些實施方案中，每條鏈的長度不超過30個核苷酸。在一些實施方案中，每條鏈的長度不超過25個核苷酸。在一些實施方案中，每條鏈的長度不超過23個核苷酸。在一些實施方案中，每條鏈的長度不超過21個核苷酸。在一些實施方案中，RNAi藥劑的有義鏈和反義鏈的長度可各自為15至49個核苷酸。在一些實施方案中，反義鏈的長度獨立地為15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30個核苷酸。在一些實施方案中，有義鏈的長度獨立地為15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35、36、37、38、39、40、41、42、43、44、45、46、47、48或49個核苷酸。在一些實施方案中，有義鏈和反義鏈的長度均為21個核苷酸。在一些實施方案中，有義鏈與反義鏈互補或基本上互補，並且互補區域的長度為15至23個核苷酸。在一些實

施方案中，互補區域的長度為19至21個核苷酸。在一些實施方案中，互補區域的長度是14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30個核苷酸。在本發明的某些實施方案中，INHBE dsRNA可包含至少一條長度為最少21個核苷酸的鏈，或者可具有基於表1至表3中的任一個表中示出的序列之一的較短雙鏈體，但與表1至表3中分別示出的dsRNA相比，在一端或兩端減去1、2、3或4個核苷酸也可能是有效的。在本發明的一些實施方案中，INHBE dsRNA藥劑可具有來自表1至表3的一個或多個序列的至少15、16、17、18、19、20個或更多個連續核苷酸的部分序列，並且這些藥劑抑制INHBE基因表達的能力與由包含完整序列的dsRNA產生的抑制水平相差不超過5%、10%、15%、20%、25%或30%。表1至表3中公開的有義序列、反義序列和雙鏈體在本文中可稱為“親本”序列，這意味著表1至表3中公開的序列可如本文所述進行修飾、縮短、延長、包括取代等，其中所得序列在本發明的方法和組合物中保留了其親本序列的全部或至少一部分功效。包含在本發明dsRNA中的有義鏈和反義鏈是獨立選擇的。如本文所用，術語“獨立選擇”意指兩個或更多個類似元件中的每一者均可獨立於其他元件的選擇而被選擇。例如，儘管並非旨在進行限制，但在製備本發明的dsRNA時，可選擇兩條鏈的“元件”以包含在雙鏈體中。一個所選的元件，有義序列可以是SEQ ID NO: 527（示於表2中），並且另一個所選的元件，反義序列可以是SEQ ID NO: 653，或者可以是與其親本序列SEQ ID NO: 653相比經過修飾、縮短、延長和/或包含1、2或3個取代的SEQ ID NO: 653。應當理解，本發明的雙鏈體不必包含表1至表3中的雙鏈體配對所示的有義序列和反義序列兩者。這些表中的每個有義鏈

序列和反義鏈序列後面緊接著其SEQ ID NO。

【0111】 本發明的組合物和方法的某些實施方案包括組合物中的和/或施用於受試者的單鏈RNA。例如，反義鏈諸如表1至表3中的任一個表中列出的反義鏈可以是組合物或施用於受試者以降低該受試者中的INHBE多肽活性和/或INHBE基因表達的組合物。表1示出了某些INHBE dsRNA藥劑反義鏈和有義鏈核心延伸鹼基序列。可包含在某些組合物中和/或在本發明的某些方法中施用的單鏈反義分子在本文中稱為“單鏈反義藥劑”或“反義多核苷酸藥劑”。可包含在某些組合物中和/或在本發明的某些方法中施用的單鏈有義分子在本文中稱為“單鏈有義藥劑”或“有義多核苷酸藥劑”。術語“鹼基序列”在本文中用於指沒有化學修飾或遞送化合物的多核苷酸序列。例如，表1所示的有義鏈GACUCUUUGCUUGAGGAUCUA（SEQ ID NO: 23）是表2中SEQ ID NO: 527和表3中SEQ ID NO: 765的鹼基序列，其中SEQ ID NO: 527和SEQ ID NO: 765與它們的化學修飾一起示出並且是遞送化合物。本文公開的序列可被分配標識符。例如，單鏈有義序列可用“有義鏈SS#”標識；單鏈反義序列可用“反義鏈AS#”標識，並且包含有義鏈和反義鏈的雙鏈體可用“雙鏈體AD#/AV#”標識。

【0112】 表1包括有義鏈和反義鏈，並提供了由表1中同一條線上的有義鏈和反義鏈形成的雙鏈體的標識編號。在本發明的某些實施方案中，反義序列包含在反義序列的位置1中的核鹼基U或核鹼基A。在本發明的某些實施方案中，反義序列包含在反義序列的位置1中的核鹼基U。如本文所用，有義鏈和反義鏈中的術語“匹配位置”是當兩條鏈為雙鏈時每條鏈中“配對”的位置。例如，在具有21個核鹼基的有義鏈和具有21個核鹼基的反義鏈中，

有義鏈的位置1中的核鹼基和反義鏈的位置21中的核鹼基處於“匹配位置”。在又一個非限制性示例中，在具有23個核鹼基的有義鏈和具有23個核鹼基的反義鏈中，有義鏈的核鹼基2和反義鏈的位置22處於匹配位置。在另一個非限制性示例中，在具有18個核鹼基的有義鏈和具有18個核鹼基的反義鏈中，有義鏈的位置1中的核鹼基和反義鏈中的核鹼基18處於匹配位置，並且有義鏈中的核鹼基4和反義鏈中的核鹼基15位於匹配位置。本領域技術人員應當理解如何標識是或者將是雙鏈和配對鏈的有義鏈和反義鏈中的匹配位置。

【0113】 表1中的第一列表示雙鏈體AV#，即包含同一表行中的有義序列和反義序列的雙鏈體。例如，表1公開了雙鏈體，即所分配的雙鏈體AV01605.um，其包含有義鏈SEQ ID NO: 23和反義鏈SEQ ID NO: 275。因此，表1中的每一行標識本發明的雙鏈體，每個雙鏈體包含同一行所示的有義序列和反義序列，其中每個雙鏈體的所分配標識符示於該行的第一列中。

【0114】 在本發明的方法的一些實施方案中，將包含表1至表3中的任一個表所示的多核苷酸序列的RNAi藥劑施用於受試者。在本發明的一些實施方案中，施用於受試者的RNAi藥劑包括雙鏈體，該雙鏈體包含表1中示出的鹼基序列中的至少一者，包括0、1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23或24個序列修飾。在本發明的方法的一些實施方案中，將包含表1至表3中的任一個表所示的多核苷酸序列的RNAi藥劑與遞送分子連接，該遞送分子的非限制性示例為包括GalNAc化合物或GLS-15*化合物的遞送化合物。

【0115】 表1：未修飾的INHBE RNAi藥劑反義鏈和有義鏈序列。所有序列均以5'至3'方向示出。雙鏈體AV#是分配給該表的同一行中的兩條鏈的雙鏈體的編號。

雙鏈體AV#	有義鏈	SEQ ID NO	反義鏈	SEQ ID NO	NM_031479.5中的位置
AV01591.um	CGUGCUGGAGCUAGCCAAGCA	9	UGCUUGGCUAGCUCCAGCACG	261	356-376
AV01592.um	GUAGCCAAGCAGCAAAUCCUA	10	UAGGAUUUGCUGCUUGGCUAC	262	366-386
AV01593.um	GCAGUCGUCCCAGAAUAACUA	11	UAGUUAUUCUGGGACGACUGC	263	403-423
AV01594.um	GCAGACUCCACUUCAGCCUAA	12	UUAGGCUGAAGUGGAGUCUGC	264	525-545
AV01595.um	GAGACUCCACUUCAGCCUACA	13	UGUAGGCUGAAGUGGAGUCUC	265	526-546
AV01596.um	GUUUUCACCUGUCCACUCCUA	14	UAGGAGUGGACAGGUGAAAAC	266	559-579
AV01597.um	CUCCCACCACCUGUACCAUGA	15	UCAUGGUACAGGUGGUGGGAG	267	581-601
AV01598.um	GCCACCCUUCCUGGCACUCUA	16	UAGAGUGCCAGGAAGGGUGGC	268	624-644
AV01599.um	GUUCCUGGCACUCUUUGCUUA	17	UAAGCAAAGAGUGCCAGGAAC	269	630-650
AV01600.um	GCCUGGCACUCUUUGCUUGAA	18	UUCAAGCAAAGAGUGCCAGGC	270	632-652
AV01601.um	GCUGGCACUCUUUGCUUGAGA	19	UCUCAAGCAAAGAGUGCCAGC	271	633-653
AV01602.um	GUGGCACUCUUUGCUUGAGGA	20	UCCUCAAGCAAAGAGUGCCAC	272	634-654
AV01603.um	CGCACUCUUUGCUUGAGGAUA	21	UAUCCUCAAGCAAAGAGUGCG	273	636-656
AV01604.um	CCACUCUUUGCUUGAGGAUCA	22	UGAUCCUCAAGCAAAGAGUGG	274	637-657
AV01605.um	GACUCUUUGCUUGAGGAUCUA	23	UAGAUCCUCAAGCAAAGAGUC	275	638-658
AV01606.um	GUGCUUGAGGAUCUUCCGAUA	24	UAUCGGAAGAUCCUCAAGCAC	276	644-664
AV01607.um	GUGCCCUCUAGUGGCUUGAGA	25	UCUCAAGCCACUAGAGGGCAC	277	747-767
AV01608.um	CGGGUGAGAAGUCUGGUGUCA	26	UGACACCAGACUUCUCACCCG	278	766-786
AV01609.um	CGUGAGAAGUCUGGUGUCCUA	27	UAGGACACCAGACUUCUCACG	279	768-788
AV01610.um	CAGAAGUCUGGUGUCCUGAAA	28	UUUCAGGACACCAGACUUCUG	280	771-791
AV01611.um	CAAGUCUGGUGUCCUGAAACA	29	UGUUUCAGGACACCAGACUUG	281	773-793
AV01612.um	GAGUCUGGUGUCCUGAAACUA	30	UAGUUUCAGGACACCAGACUC	282	774-794
AV01613.um	CGUGUCCUGAAACUGCAACUA	31	UAGUUGCAGUUUCAGGACACG	283	780-800
AV01614.um	CUGUCCUGAAACUGCAACUAA	32	UUAGUUGCAGUUUCAGGACAG	284	781-801

AV01615.um	GGUCCUGAAACUGC AACUAGA	33	UCUAGUUGCAGUU UCAGGACC	285	782-802
AV01616.um	CUCCUGAAACUGCA ACUAGAA	34	UUCUAGUUGCAGU UUCAGGAG	286	783-803
AV01617.um	GCCUGAAACUGCAA CUAGACA	35	UGUCUAGUUGCAG UUUCAGGC	287	784-804
AV01618.um	GCUGAAACUGCAAC UAGACUA	36	UAGUCUAGUUGCA GUUUCAGC	288	785-805
AV01619.um	CAAACUGCAACUAG ACUGCAA	37	UUGCAGUCUAGUU GCAGUUUG	289	788-808
AV01620.um	GACUGCAACUAGAC UGCAGAA	38	UUCUGCAGUCUAG UUGCAGUC	290	790-810
AV01621.um	GACAGCACAGUUAC UGGACAA	39	UUGUCCAGUAACU GUGCUGUC	291	822-842
AV01622.um	GCUUCCUAGAGCUU AAGAUCA	40	UGAUCUUAAGCUC UAGGAAGC	292	880-900
AV01623.um	GUUCCUAGAGCUUA AGAUCCA	41	UGGAUCUUAAGCU CUAGGAAC	293	881-901
AV01624.um	CAGCUUAAGAUCCG AGCCAAA	42	UUUGGCUCGGAUC UUAAGCUG	294	888-908
AV01625.um	GGCUUAAGAUCCGA GCCAAUA	43	UAUUGGCUCGGAU CUUAAGCC	295	889-909
AV01626.um	GUGCGACCCCCUUA UGUUGCA	44	UGCAACAUAAGGG GGUCGCAC	296	955-975
AV01627.um	GGCGACCCCCUUAU GUUGCAA	45	UUGCAACAUAAGG GGGUCGCC	297	956-976
AV01628.um	CAGACCAUUACGUA GACUUCA	46	UGAAGUCUACGUA AUGGUCUG	298	979-999
AV01629.um	GGACCAUUACGUAG ACUUCCA	47	UGGAAGUCUACGU AAUGGUCC	299	980-1000
AV01630.um	GUACGUAGACUUCC AGGAACA	48	UGUUCCUGGAAGU CUACGUAC	300	986-1006
AV01631.um	GACGUAGACUUCCA GGAACUA	49	UAGUUCCUGGAAG UCUACGUC	301	987-1007
AV01632.um	CGGGUACCAGCUGA AUUACUA	50	UAGUAAUUCAGCU GGUACCCG	302	1037-1057
AV01633.um	CUACCAGCUGAAUU ACUGCAA	51	UUGCAGUAAUUCA GCUGGUAG	303	1040-1060
AV01634.um	GAUUGCUGCCUCUU UCCAUUA	52	UAAUGGAAAGAGG CAGCAAUC	304	1097-1117
AV01635.um	GUUGCUGCCUCUUU CCAUUCA	53	UGAAUGGAAAGAG GCAGCAAC	305	1098-1118
AV01636.um	GUGCUGCCUCUUUC CAUUCUA	54	UAGAAUGGAAAGA GGCAGCAC	306	1099-1119
AV01637.um	GGCUGCCUCUUUCC AUUCUGA	55	UCAGAAUGGAAAG AGGCAGCC	307	1100-1120
AV01638.um	GCUUUCCAUUCUGC CGUCUUA	56	UAAGACGGCAGAA UGGAAAGC	308	1107-1127
AV01639.um	GGUCUUCAGCCUCC UCAAAGA	57	UCUUUGAGGAGGC UGAAGACC	309	1121-1141
AV01640.um	GUCCUCAAAGCCAA CAAUCCA	58	UGGAUUGUUGGCU UUGAGGAC	310	1131-1151
AV01641.um	GCCUCAAAGCCAAC AAUCCUA	59	UAGGAUUGUUGGC UUUGAGGC	311	1132-1152
AV01642.um	GAUCCUUGGCCUGC CAGUACA	60	UGUACUGGCAGGC CAAGGAUC	312	1146-1166
AV01643.um	GUCUCCUCUACCUG GAUCAUA	61	UAUGAUCCAGGUA GAGGAGAC	313	1201-1221

AV01644.um	GCUCCUCUACCUGG AUCAUAA	62	UUAUGAUCCAGGU AGAGGAGC	314	1202-1222
AV01645.um	GUCCUCUACCUGGA UCAUAAA	63	UUUAUGAUCCAGG UAGAGGAC	315	1203-1223
AV01646.um	GCUCUACCUGGAUC AUAAUGA	64	UCAUUAUGAUCCA GGUAGAGC	316	1205-1225
AV01647.um	GUGGAUCAUAAUGG CAAUGUA	65	UACAUUGCCAUUA UGAUCCAC	317	1212-1232
AV01648.um	GGGAUCAUAAUGGC AAUGUGA	66	UCACAUUGCCAUU AUGAUCCC	318	1213-1233
AV01649.um	CGAUCAUAAUGGCA AUGUGGA	67	UCCACAUUGCCAU UAUGAUCG	319	1214-1234
AV01650.um	GAUAAUGGCAAUGU GGUCAAA	68	UUUGACCACAUUG CCAUUAUC	320	1218-1238
AV01651.um	GAAUGGCAAUGUGG UCAAGAA	69	UUCUUGACCACAU UGCCAUUC	321	1220-1240
AV01652.um	GAAGACGGAUGUGC CAGAUAA	70	UUAUCUGGCACAU CCGUCUUC	322	1235-1255
AV01653.um	CAUGUGCCAGAUAU GGUGGUA	71	UACCACCAUAUCU GGCACAUG	323	1242-1262
AV01654.um	CUGGCUGCAGCUAG CAAGAGA	72	UCUCUUGCUAGCU GCAGCCAG	324	1270-1290
AV01655.um	CCAAGAGGACCUGG GGCUUUA	73	UAAAGCCCCAGGU CCUCUUGG	325	1283-1303
AV01656.um	GUGGAGUGAAGAGA CCAAGAA	74	UUCUUGGUCUCUU CACUCCAC	326	1301-1321
AV01657.um	CGAGUGAAGAGACC AAGAUGA	75	UCAUCUUGGUCUC UUCACUCG	327	1303-1323
AV01658.um	CAGUGAAGAGACCA AGAUGAA	76	UUCAUCUUGGUCU CUUCACUG	328	1304-1324
AV01659.um	GGAAGAGACCAAGA UGAAGUA	77	UACUUCAUCUUGG UCUCUUCC	329	1307-1327
AV01660.um	GAGAGACCAAGAUG AAGUUUA	78	UAAACUUCAUCUU GGUCUCUC	330	1309-1329
AV01661.um	GGAGACCAAGAUGA AGUUUCA	79	UGAAACUUCAUCU UGGUCUCC	331	1310-1330
AV01662.um	CACCAAGAUGAAGU UUCCCAA	80	UUGGGAAACUUCA UCUUGGUG	332	1313-1333
AV01663.um	CACUGGAGGCAUCA GAUUCCA	81	UGGAAUCUGAUGC CUCCAGUG	333	1349-1369
AV01664.um	GAACAACCACCUGG CAAUAUA	82	UAUAUUGCCAGGU GGUUGUUC	334	1386-1406
AV01665.um	GACAACCACCUGGC AAUAUGA	83	UCAUAUUGCCAGG UGGUUGUC	335	1387-1407
AV01666.um	GCAACCACCUGGCA AUAUGAA	84	UUCAUAUUGCCAG GUGGUUGC	336	1388-1408
AV01667.um	GCCUGGCAAUAUGA CUCACUA	85	UAGUGAGUCAUAU UGCCAGGC	337	1394-1414
AV01668.um	GCUGGCAAUAUGAC UCACUUA	86	UAAGUGAGUCAUA UUGCCAGC	338	1395-1415
AV01669.um	GUGGCAAUAUGACU CACUUGA	87	UCAAGUGAGUCAU AUUGCCAC	339	1396-1416
AV01670.um	CGCAAUAUGACUCA CUUGACA	88	UGUCAAGUGAGUC AUAUUGCG	340	1398-1418
AV01671.um	GUGACUCACUUGAC CCCUAUA	89	UAUAGGGGUCAAG UGAGUCAC	341	1404-1424
AV01672.um	GCAAAUGGGCACUU UCUUGUA	90	UACAAGAAAGUGC CCAUUUGC	342	1429-1449

AV01673.um	GAAAUGGGCACUUU CUUGUCA	91	UGACAAGAAAGUG CCCAUUUC	343	1430-1450
AV01674.um	GAAUGGGCACUUUC UUGUCUA	92	UAGACAAGAAAGU GCCCAUUC	344	1431-1451
AV01675.um	GAUGGGCACUUUCU UGUCUGA	93	UCAGACAAGAAAG UGCCCAUC	345	1432-1452
AV01676.um	GUGGGCACUUUCUU GUCUGAA	94	UUCAGACAAGAAA GUGCCCAC	346	1433-1453
AV01677.um	CGGCACUUUCUUGU CUGAGAA	95	UUCUCAGACAAGA AAGUGCCG	347	1435-1455
AV01678.um	CGCACUUUCUUGUC UGAGACA	96	UGUCUCAGACAAG AAAGUGCG	348	1436-1456
AV01679.um	CCACUUUCUUGUCU GAGACUA	97	UAGUCUCAGACAA GAAAGUGG	349	1437-1457
AV01680.um	GCUUUCUUGUCUGA GACUCUA	98	UAGAGUCUCAGAC AAGAAAGC	350	1439-1459
AV01681.um	GUAUUCCAGGUUGG CUGAUGA	99	UCAUCAGCCAACC UGGAAUAC	351	1462-1482
AV01682.um	GCCAGGUUGGCUGA UGUGUUA	100	UAACACAUCAGCC AACCUGGC	352	1466-1486
AV01683.um	CUUUCUUCUAAAGG GGUCUAA	101	UUAGACCCCUUUA GAAGAAAG	353	1502-1522
AV01684.um	GACUUAGCCUCUCCC AAGAUA	102	UAUCUUGGGAGAG GCUAAGUC	354	1605-1625
AV01685.um	GCUCUCCCAAGAUG AGAAAGA	103	UCUUUCUCAUCUU GGGAGAGC	355	1612-1632
AV01686.um	GUCUCCCAAGAUGA GAAAGUA	104	UACUUUCUCAUCU UGGGAGAC	356	1613-1633
AV01687.um	GCUCCCAAGAUGAG AAAGUCA	105	UGACUUUCUCAUC UUGGGAGC	357	1614-1634
AV01688.um	CAGGAGGAAGCAGA UAGAUGA	106	UCAUCUAUCUGCU UCCUCCUG	358	1646-1666
AV01689.um	CGAGGAAGCAGAUA GAUGGUA	107	UACCAUCUAUCUG CUUCCUCG	359	1648-1668
AV01690.um	CAGGAAGCAGAUAG AUGGUCA	108	UGACCAUCUAUCU GCUUCCUG	360	1649-1669
AV01691.um	CUCCAGCAGGCUUG AAGCAGA	109	UCUGCUUCAAGCC UGCUGGAG	361	1666-1686
AV01692.um	GAGAAACAGGAGUC AGGAAAA	110	UUUUCCUGACUCC UGUUUCUC	362	1786-1806
AV01693.um	CAGGCACUAAGCCU AAGAAGA	111	UCUUCUUAGGCUU AGUGCCUG	363	1808-1828
AV01694.um	CGCACUAAGCCUAA GAAGUUA	112	UAACUUCUUAGGC UUAGUGCG	364	1810-1830
AV01695.um	CCACUAAGCCUAAG AAGUUCA	113	UGAACUUCUUAGG CUUAGUGG	365	1811-1831
AV01696.um	GCAGGACCCACUGG GAGACAA	114	UUGUCUCCCAGUG GGUCCUGC	366	1849-1869
AV01697.um	GACUGGGAGACAAG CAUUUAA	115	UUAAAUGCUUGUC UCCCAGUC	367	1857-1877
AV01698.um	CGGAGACAAGCAUU UAUACUA	116	UAGUAUAAAUGCU UGUCUCCG	368	1861-1881
AV01699.um	CGAGACAAGCAUUU AUACUUA	117	UAAGUAUAAAUGC UUGUCUCG	369	1862-1882
AV01700.um	GGACAAGCAUUUAU ACUUUCA	118	UGAAAGUAUAAAU GCUUGUCC	370	1864-1884
AV01701.um	CACAAGCAUUUAUA CUUUCUA	119	UAGAAAGUAUAAA UGCUUGUG	371	1865-1885

AV01702.um	GCAAGCAUUUAUACUUUCUUA	120	UAAGAAAGUAUAAAUGCUUGC	372	1866-1886
AV01703.um	GAGGCGCCCACUAAUUUUUGA	121	UCAAAAAUUAGUGGGCGCCUC	373	2026-2046
AV01704.um	GGCCUGGCUUAUACUUUCUUA	122	UAAGAAAGUAUAAGCCAGGCC	374	2162-2182
AV01705.um	CCCUGGCUUAUACUUUCUUAA	123	UUAAGAAAGUAUAAGCCAGGG	375	2163-2183
AV01706.um	GUGGCUUAUACUUUCUUAAUA	124	UAUUAAGAAAGUAUAAGCCAC	376	2165-2185
AV01707.um	GGGCUUAUACUUUCUUAAUAA	125	UUAUUAAGAAAGUAUAAGCCC	377	2166-2186
AV01708.um	CGCUUAUACUUUCUUAAUAAA	126	UUUAUUAAGAAAGUAUAAGCG	378	2167-2187
AV01709.um	GUUUCUUAAUAAAAAGGAGAA	127	UUCUCCUUUUUAUUAAGAAAC	379	2175-2195
AV01710.um	GUUCUUAAUAAAAAGGAGAAA	128	UUUCUCCUUUUUAUUAAGAAC	380	2176-2196
AV03974.um	CAAGCAUUUAUACUUUCUUUU	129	AAAAGAAAGUAUAAAUGCUUG	381	1867-1887
AV03975.um	CCAGUCGUCCCAGAAUAACUU	130	AAGUUAUUCUGGGACGACUGG	382	403-423
AV03976.um	ACAGACGGAGCAACUGCCAUU	131	AAUGGCAGUUGCUCCGUCUGU	383	176-196
AV03977.um	UCCCAGAAUAACUCAUCCUCU	132	AGAGGAUGAGUUAUUCUGGGA	384	410-430
AV03978.um	CCAGGUUGGCUGAUGUGUUGU	133	ACAACACAUCAGCCAACCUGG	385	1467-1487
AV03979.um	GAUUUCCUGCCCUAAGUCCUU	134	AAGGACUUAGGGCAGGAAAUC	386	1534-1554
AV01591-19.um	UGCUGGAGCUAGCCAAGCA	135	UGCUUGGCUAGCUCCAGCA	387	358-376
AV01592-19.um	AGCCAAGCAGCAAAUCCUA	136	UAGGAUUUGCUGCUUGGCU	388	368-386
AV01593-19.um	AGUCGUCCCAGAAUAACUA	137	UAGUUAUUCUGGGACGACU	389	405-423
AV01594-19.um	AGACUCCACUUCAGCCUAA	138	UUAGGCUGAAGUGGAGUCU	390	527-545
AV01595-19.um	GACUCCACUUCAGCCUACA	139	UGUAGGCUGAAGUGGAGUC	391	528-546
AV01596-19.um	UUUCACCUGUCCACUCCUA	140	UAGGAGUGGACAGGUGAAA	392	561-579
AV01597-19.um	CCCACCACCUGUACCAUGA	141	UCAUGGUACAGGUGGUGGG	393	583-601
AV01598-19.um	CACCCUUCCUGGCACUCUA	142	UAGAGUGCCAGGAAGGGUG	394	626-644
AV01599-19.um	UCCUGGCACUCUUUGCUUA	143	UAAGCAAAGAGUGCCAGGA	395	632-650
AV01600-19.um	CUGGCACUCUUUGCUUGAA	144	UUCAAGCAAAGAGUGCCAG	396	634-652
AV01601-19.um	UGGCACUCUUUGCUUGAGA	145	UCUCAAGCAAAGAGUGCCA	397	635-653
AV01602-19.um	GGCACUCUUUGCUUGAGGA	146	UCCUCAAGCAAAGAGUGCC	398	636-654
AV01603-19.um	CACUCUUUGCUUGAGGAUA	147	UAUCCUCAAGCAAAGAGUG	399	638-656
AV01604-19.um	ACUCUUUGCUUGAGGAUCA	148	UGAUCCUCAAGCAAAGAGU	400	639-657

AV01605-19.um	CUCUUUGCUUGAGGAUCUA	149	UAGAUCCUCAAGCAAAGAG	401	640-658
AV01606-19.um	GCUUGAGGAUCUUCCGAUA	150	UAUCGGAAGAUCCUCAAGC	402	646-664
AV01607-19.um	GCCCUCUAGUGGCUUGAGA	151	UCUCAAGCCACUAGAGGGC	403	749-767
AV01608-19.um	GGUGAGAAGUCUGGUGUCA	152	UGACACCAGACUUCUCACC	404	768-786
AV01609-19.um	UGAGAAGUCUGGUGUCCUA	153	UAGGACACCAGACUUCUCA	405	770-788
AV01610-19.um	GAAGUCUGGUGUCCUGAAA	154	UUUCAGGACACCAGACUUC	406	773-791
AV01611-19.um	AGUCUGGUGUCCUGAAACA	155	UGUUUCAGGACACCAGACU	407	775-793
AV01612-19.um	GUCUGGUGUCCUGAAACUA	156	UAGUUUCAGGACACCAGAC	408	776-794
AV01613-19.um	UGUCCUGAAACUGCAACUA	157	UAGUUGCAGUUUCAGGACA	409	782-800
AV01614-19.um	GUCCUGAAACUGCAACUAA	158	UUAGUUGCAGUUUCAGGAC	410	783-801
AV01615-19.um	UCCUGAAACUGCAACUAGA	159	UCUAGUUGCAGUUUCAGGA	411	784-802
AV01616-19.um	CCUGAAACUGCAACUAGAA	160	UUCUAGUUGCAGUUUCAGG	412	785-803
AV01617-19.um	CUGAAACUGCAACUAGACA	161	UGUCUAGUUGCAGUUUCAG	413	786-804
AV01618-19.um	UGAAACUGCAACUAGACUA	162	UAGUCUAGUUGCAGUUUCA	414	787-805
AV01619-19.um	AACUGCAACUAGACUGCAA	163	UUGCAGUCUAGUUGCAGUU	415	790-808
AV01620-19.um	CUGCAACUAGACUGCAGAA	164	UUCUGCAGUCUAGUUGCAG	416	792-810
AV01621-19.um	CAGCACAGUUACUGGACAA	165	UUGUCCAGUAACUGUGCUG	417	824-842
AV01622-19.um	UUCCUAGAGCUUAAGAUCA	166	UGAUCUUAAGCUCUAGGAA	418	882-900
AV01623-19.um	UCCUAGAGCUUAAGAUCCA	167	UGGAUCUUAAGCUCUAGGA	419	883-901
AV01624-19.um	GCUUAAGAUCCGAGCCAAA	168	UUUGGCUCGGAUCUUAAGC	420	890-908
AV01625-19.um	CUUAAGAUCCGAGCCAAUA	169	UAUUGGCUCGGAUCUUAAG	421	891-909
AV01626-19.um	GCGACCCCCUUAUGUUGCA	170	UGCAACAUAAGGGGGUCGC	422	957-975
AV01627-19.um	CGACCCCCUUAUGUUGCAA	171	UUGCAACAUAAGGGGGUCG	423	958-976
AV01628-19.um	GACCAUUACGUAGACUUCA	172	UGAAGUCUACGUAAUGGUC	424	981-999
AV01629-19.um	ACCAUUACGUAGACUUCCA	173	UGGAAGUCUACGUAAUGGU	425	982-1000
AV01630-19.um	ACGUAGACUUCCAGGAACA	174	UGUUCCUGGAAGUCUACGU	426	988-1006
AV01631-19.um	CGUAGACUUCCAGGAACUA	175	UAGUUCCUGGAAGUCUACG	427	989-1007
AV01632-19.um	GGUACCAGCUGAAUUACUA	176	UAGUAAUUCAGCUGGUACC	428	1039-1057
AV01633-19.um	ACCAGCUGAAUUACUGCAA	177	UUGCAGUAAUUCAGCUGGU	429	1042-1060

AV01634-19.um	UUGCUGCCUCUUUCCAUUA	178	UAAUGGAAAGAGGCAGCAA	430	1099-1117
AV01635-19.um	UGCUGCCUCUUUCCAUUCA	179	UGAAUGGAAAGAGGCAGCA	431	1100-1118
AV01636-19.um	GCUGCCUCUUUCCAUUCUA	180	UAGAAUGGAAAGAGGCAGC	432	1101-1119
AV01637-19.um	CUGCCUCUUUCCAUUCUGA	181	UCAGAAUGGAAAGAGGCAG	433	1102-1120
AV01638-19.um	UUUCCAUUCUGCCGUCUUA	182	UAAGACGGCAGAAUGGAAA	434	1109-1127
AV01639-19.um	UCUUCAGCCUCCUCAAAGA	183	UCUUUGAGGAGGCUGAAGA	435	1123-1141
AV01640-19.um	CCUCAAAGCCAACAAUCCA	184	UGGAUUGUUGGCUUUGAGG	436	1133-1151
AV01641-19.um	CUCAAAGCCAACAAUCCUA	185	UAGGAUUGUUGGCUUUGAG	437	1134-1152
AV01642-19.um	UCCUUGGCCUGCCAGUACA	186	UGUACUGGCAGGCCAAGGA	438	1148-1166
AV01643-19.um	CUCCUCUACCUGGAUCAUA	187	UAUGAUCCAGGUAGAGGAG	439	1203-1221
AV01644-19.um	UCCUCUACCUGGAUCAUAA	188	UUAUGAUCCAGGUAGAGGA	440	1204-1222
AV01645-19.um	CCUCUACCUGGAUCAUAAA	189	UUUAUGAUCCAGGUAGAGG	441	1205-1223
AV01646-19.um	UCUACCUGGAUCAUAAUGA	190	UCAUUAUGAUCCAGGUAGA	442	1207-1225
AV01647-19.um	GGAUCAUAAUGGCAAUGUA	191	UACAUUGCCAUUAUGAUCC	443	1214-1232
AV01648-19.um	GAUCAUAAUGGCAAUGUGA	192	UCACAUUGCCAUUAUGAUC	444	1215-1233
AV01649-19.um	AUCAUAAUGGCAAUGUGGA	193	UCCACAUUGCCAUUAUGAU	445	1216-1234
AV01650-19.um	UAAUGGCAAUGUGGUCAAA	194	UUUGACCACAUUGCCAUUA	446	1220-1238
AV01651-19.um	AUGGCAAUGUGGUCAAGAA	195	UUCUUGACCACAUUGCCAU	447	1222-1240
AV01652-19.um	AGACGGAUGUGCCAGAUAA	196	UUAUCUGGCACAUCCGUCU	448	1237-1255
AV01653-19.um	UGUGCCAGAUAUGGUGGUA	197	UACCACCAUAUCUGGCACA	449	1244-1262
AV01654-19.um	GGCUGCAGCUAGCAAGAGA	198	UCUCUUGCUAGCUGCAGCC	450	1272-1290
AV01655-19.um	AAGAGGACCUGGGGCUUUA	199	UAAAGCCCCAGGUCCUCUU	451	1285-1303
AV01656-19.um	GGAGUGAAGAGACCAAGAA	200	UUCUUGGUCUCUUCACUCC	452	1303-1321
AV01657-19.um	AGUGAAGAGACCAAGAUGA	201	UCAUCUUGGUCUCUUCACU	453	1305-1323
AV01658-19.um	GUGAAGAGACCAAGAUGAA	202	UUCAUCUUGGUCUCUUCAC	454	1306-1324
AV01659-19.um	AAGAGACCAAGAUGAAGUA	203	UACUUCAUCUUGGUCUCUU	455	1309-1327
AV01660-19.um	GAGACCAAGAUGAAGUUUA	204	UAAACUUCAUCUUGGUCUC	456	1311-1329
AV01661-19.um	AGACCAAGAUGAAGUUUCA	205	UGAAACUUCAUCUUGGUCU	457	1312-1330
AV01662-19.um	CCAAGAUGAAGUUUCCCAA	206	UUGGGAAACUUCAUCUUGG	458	1315-1333

AV01663-19.um	CUGGAGGCAUCAGAUUCCA	207	UGGAAUCUGAUGCCUCCAG	459	1351-1369
AV01664-19.um	ACAACCACCUGGCAAUAUA	208	UAUAUUGCCAGGUGGUUGU	460	1388-1406
AV01665-19.um	CAACCACCUGGCAAUAUGA	209	UCAUAUUGCCAGGUGGUUG	461	1389-1407
AV01666-19.um	AACCACCUGGCAAUAUGAA	210	UUCAUAUUGCCAGGUGGUU	462	1390-1408
AV01667-19.um	CUGGCAAUAUGACUCACUA	211	UAGUGAGUCAUAUUGCCAG	463	1396-1414
AV01668-19.um	UGGCAAUAUGACUCACUUA	212	UAAGUGAGUCAUAUUGCCA	464	1397-1415
AV01669-19.um	GGCAAUAUGACUCACUUGA	213	UCAAGUGAGUCAUAUUGCC	465	1398-1416
AV01670-19.um	CAAUAUGACUCACUUGACA	214	UGUCAAGUGAGUCAUAUUG	466	1400-1418
AV01671-19.um	GACUCACUUGACCCCUAUA	215	UAUAGGGGUCAAGUGAGUC	467	1406-1424
AV01672-19.um	AAAUGGGCACUUUCUUGUA	216	UACAAGAAAGUGCCCAUUU	468	1431-1449
AV01673-19.um	AAUGGGCACUUUCUUGUCA	217	UGACAAGAAAGUGCCCAUU	469	1432-1450
AV01674-19.um	AUGGGCACUUUCUUGUCUA	218	UAGACAAGAAAGUGCCCAU	470	1433-1451
AV01675-19.um	UGGGCACUUUCUUGUCUGA	219	UCAGACAAGAAAGUGCCCA	471	1434-1452
AV01676-19.um	GGGCACUUUCUUGUCUGAA	220	UUCAGACAAGAAAGUGCCC	472	1435-1453
AV01677-19.um	GCACUUUCUUGUCUGAGAA	221	UUCUCAGACAAGAAAGUGC	473	1437-1455
AV01678-19.um	CACUUUCUUGUCUGAGACA	222	UGUCUCAGACAAGAAAGUG	474	1438-1456
AV01679-19.um	ACUUUCUUGUCUGAGACUA	223	UAGUCUCAGACAAGAAAGU	475	1439-1457
AV01680-19.um	UUUCUUGUCUGAGACUCUA	224	UAGAGUCUCAGACAAGAAA	476	1441-1459
AV01681-19.um	AUUCCAGGUUGGCUGAUGA	225	UCAUCAGCCAACCUGGAAU	477	1464-1482
AV01682-19.um	CAGGUUGGCUGAUGUGUUA	226	UAACACAUCAGCCAACCUG	478	1468-1486
AV01683-19.um	UUCUUCUAAAGGGGUCUAA	227	UUAGACCCCUUUAGAAGAA	479	1504-1522
AV01684-19.um	CUUAGCCUCUCCCAAGAUA	228	UAUCUUGGGAGAGGCUAAG	480	1607-1625
AV01685-19.um	UCUCCCAAGAUGAGAAAGA	229	UCUUUCUCAUCUUGGGAGA	481	1614-1632
AV01686-19.um	CUCCCAAGAUGAGAAAGUA	230	UACUUUCUCAUCUUGGGAG	482	1615-1633
AV01687-19.um	UCCCAAGAUGAGAAAGUCA	231	UGACUUUCUCAUCUUGGGA	483	1616-1634
AV01688-19.um	GGAGGAAGCAGAUAGAUGA	232	UCAUCUAUCUGCUUCCUCC	484	1648-1666
AV01689-19.um	AGGAAGCAGAUAGAUGGUA	233	UACCAUCUAUCUGCUUCCU	485	1650-1668
AV01690-19.um	GGAAGCAGAUAGAUGGUCA	234	UGACCAUCUAUCUGCUUCC	486	1651-1669
AV01691-19.um	CCAGCAGGCUUGAAGCAGA	235	UCUGCUUCAAGCCUGCUGG	487	1668-1686

AV01692-19.um	GAAACAGGAGUCAGGAAAA	236	UUUUCCUGACUCCUGUUUC	488	1788-1806
AV01693-19.um	GGCACUAAGCCUAAGAAGA	237	UCUUCUUAGGCUUAGUGCC	489	1810-1828
AV01694-19.um	CACUAAGCCUAAGAAGUUA	238	UAACUUCUUAGGCUUAGUG	490	1812-1830
AV01695-19.um	ACUAAGCCUAAGAAGUUCA	239	UGAACUUCUUAGGCUUAGU	491	1813-1831
AV01696-19.um	AGGACCCACUGGGAGACAA	240	UUGUCUCCCAGUGGGUCCU	492	1851-1869
AV01697-19.um	CUGGGAGACAAGCAUUUAA	241	UUAAAUGCUUGUCUCCCAG	493	1859-1877
AV01698-19.um	GAGACAAGCAUUUAUACUA	242	UAGUAUAAAUGCUUGUCUC	494	1863-1881
AV01699-19.um	AGACAAGCAUUUAUACUUA	243	UAAGUAUAAAUGCUUGUCU	495	1864-1882
AV01700-19.um	ACAAGCAUUUAUACUUUCA	244	UGAAAGUAUAAAUGCUUGU	496	1866-1884
AV01701-19.um	CAAGCAUUUAUACUUUCUA	245	UAGAAAGUAUAAAUGCUUG	497	1867-1885
AV01702-19.um	AAGCAUUUAUACUUUCUUA	246	UAAGAAAGUAUAAAUGCUU	498	1868-1886
AV01703-19.um	GGCGCCCACUAAUUUUUGA	247	UCAAAAAUUAGUGGGCGCC	499	2028-2046
AV01704-19.um	CCUGGCUUAUACUUUCUUA	248	UAAGAAAGUAUAAGCCAGG	500	2164-2182
AV01705-19.um	CUGGCUUAUACUUUCUUAA	249	UUAAGAAAGUAUAAGCCAG	501	2165-2183
AV01706-19.um	GGCUUAUACUUUCUUAAUA	250	UAUUAAGAAAGUAUAAGCC	502	2167-2185
AV01707-19.um	GCUUAUACUUUCUUAAUAA	251	UUAUUAAGAAAGUAUAAGC	503	2168-2186
AV01708-19.um	CUUAUACUUUCUUAAUAAA	252	UUUAUUAAGAAAGUAUAAG	504	2169-2187
AV01709-19.um	UUCUUAAUAAAAAGGAGAA	253	UUCUCCUUUUUAUUAAGAA	505	2177-2195
AV01710-19.um	UCUUAAUAAAAAGGAGAAA	254	UUUCUCCUUUUUAUUAAGA	506	2178-2196
AV03974-19.um	AGCAUUUAUACUUUCUUUU	255	AAAAGAAAGUAUAAAUGCU	507	1869-1887
AV03975-19.um	AGUCGUCCCAGAAUAACUU	256	AAGUUAUUCUGGGACGACU	508	405-423
AV03976-19.um	AGACGGAGCAACUGCCAUU	257	AAUGGCAGUUGCUCCGUCU	509	178-196
AV03977-19.um	CCAGAAUAACUCAUCCUCU	258	AGAGGAUGAGUUAUUCUGG	510	412-430
AV03978-19.um	AGGUUGGCUGAUGUGUUGU	259	ACAACACAUCAGCCAACCU	511	1469-1487
AV03979-19.um	UUUCCUGCCCUAAGUCCUU	260	AAGGACUUAGGGCAGGAAA	512	1536-1554
AV05265.um	GACUUUUCACCUGUCCACUCA	851	UGAGUGGACAGGUGAAAAGUC	1037	557-577
AV05270.um	GCUCUGCCCUCUAGUGGCUUA	852	UAAGCCACUAGAGGGCAGAGC	1038	744-764
AV05279.um	CCUUAAGAUCCGAGCCAAUGA	853	UCAUUGGCUCGGAUCUUAAGG	1039	890-910
AV05280.um	CGACCCCCACCUGUGAGCCUA	854	UAGGCUCACAGGUGGGGGUCG	1040	937-957

AV05283.um	GGACCCCCUUAUGUUGCAGGA	855	UCCUGCAACAUAAGGGGGUCC	1041	958-978
AV05286.um	GUUACGUAGACUUCCAGGAAA	856	UUUCCUGGAAGUCUACGUAAC	1042	985-1005
AV05290.um	CGACCUGGGGCUUUGGAGUGA	857	UCACUCCAAAGCCCCAGGUCG	1043	1289-1309
AV05291.um	CACCUGGGGCUUUGGAGUGAA	858	UUCACUCCAAAGCCCCAGGUG	1044	1290-1310
AV05294.um	GAAUAUGACUCACUUGACCCA	859	UGGGUCAAGUGAGUCAUAUUC	1045	1400-1420
AV05295.um	GAUGACUCACUUGACCCCUAA	860	UUAGGGGUCAAGUGAGUCAUC	1046	1403-1423
AV05304.um	CCCUAAGAAGUUCCCUGGUUA	861	UAACCAGGGAACUUCUUAGGG	1047	1818-1838
AV05305.um	GAGUUCCCUGGUUUUUCCCAA	862	UUGGGAAAAACCAGGGAACUC	1048	1825-1845
AV05306.um	GGUUCCCUGGUUUUUCCCAGA	863	UCUGGGAAAAACCAGGGAACC	1049	1826-1846
AV05308.um	GGAAACGAGGUUUCAACAUGA	864	UCAUGUUGAAACCUCGUUUCC	1050	2056-2076
AV05313.um	GUUAUACUUUCUUAAUAAAAA	865	UUUUUAUUAAGAAAGUAUAAC	1051	2169-2189
AV05314.um	GACUUUCUUAAUAAAAAGGAA	866	UUCCUUUUUAUUAAGAAAGUC	1052	2173-2193
AV05315.um	GUCUUAAUAAAAAGGAGAAAA	867	UUUUCUCCUUUUUAUUAAGAC	1053	2177-2197
AV05316.um	GCUUAAUAAAAAGGAGAAAGA	868	UCUUUCUCCUUUUUAUUAAGC	1054	2178-2198
AV06796.um	CUGCUGGAGCUAGCCAAGCAA	869	UUGCUUGGCUAGCUCCAGCAG	1055	357-377
AV06797.um	CCCAAGCAGCAAAUCCUGGAA	870	UUCCAGGAUUUGCUGCUUGGG	1056	369-389
AV06798.um	GAGUCGUCCCAGAAUAACUCA	871	UGAGUUAUUCUGGGACGACUC	1057	404-424
AV06799.um	CACCAGAGCCCUCCGGAGACA	872	UGUCUCCGGAGGGCUCUGGUG	1058	446-466
AV06800.um	CAGGUCAUCAGCUUUGCUACA	873	UGUAGCAAAGCUGAUGACCUG	1059	501-521
AV06801.um	GACCUGUCCACUCCUCGGUCA	874	UGACCGAGGAGUGGACAGGUC	1060	564-584
AV06802.um	GUGUCCACUCCUCGGUCCCAA	875	UUGGGACCGAGGAGUGGACAC	1061	567-587
AV06803.um	GCCACCACCUGUACCAUGCCA	876	UGGCAUGGUACAGGUGGUGGC	1062	583-603
AV06804.um	CCUCCCCACCCUUCCUGGCAA	877	UUGCCAGGAAGGGUGGGGAGG	1063	620-640
AV06805.um	GUCCCCACCCUUCCUGGCACA	878	UGUGCCAGGAAGGGUGGGGAC	1064	621-641
AV06806.um	GCUCUUUGCUUGAGGAUCUUA	879	UAAGAUCCUCAAGCAAAGAGC	1065	639-659
AV06807.um	GUUGAGGAUCUUCCGAUGGGA	880	UCCCAUCGGAAGAUCCUCAAC	1066	647-667
AV06808.um	CGAUCUUCCGAUGGGGACCAA	881	UUGGUCCCCAUCGGAAGAUCG	1067	652-672
AV06809.um	GUGGCUGAGCACCACAUCACA	882	UGUGAUGUGGUGCUCAGCCAC	1068	702-722
AV06810.um	CAGCACCACAUCACCAACCUA	883	UAGGUUGGUGAUGUGGUGCUG	1069	708-728

AV06811.um	CCACCACAUCACCAA CCUGGA	884	UCCAGGUUGGUGA UGUGGUGG	1070	710-730
AV06812.um	GAUACCUUAACUCU GCCCUCA	885	UGAGGGCAGAGUU AAGGUAUC	1071	735-755
AV06813.um	GUACCUUAACUCUG CCCUCUA	886	UAGAGGGCAGAGU UAAGGUAC	1072	736-756
AV06814.um	CCCCUCUAGUGGCU UGAGGGA	887	UCCCUCAAGCCAC UAGAGGGG	1073	749-769
AV06815.um	GCUCUAGUGGCUUG AGGGGUA	888	UACCCCUCAAGCC ACUAGAGC	1074	751-771
AV06816.um	CGGUGAGAAGUCUG GUGUCCA	889	UGGACACCAGACU UCUCACCG	1075	767-787
AV06817.um	CUCUGGUGUCCUGA AACUGCA	890	UGCAGUUUCAGGA CACCAGAG	1076	776-796
AV06818.um	GCUGGUGUCCUGAA ACUGCAA	891	UUGCAGUUUCAGG ACACCAGC	1077	777-797
AV06819.um	GUGGUGUCCUGAAA CUGCAAA	892	UUUGCAGUUUCAG GACACCAC	1078	778-798
AV06820.um	GCUGCAGACCCCUA GAAGGCA	893	UGCCUUCUAGGGG UCUGCAGC	1079	802-822
AV06821.um	GUGCAGACCCCUAG AAGGCAA	894	UUGCCUUCUAGGG GUCUGCAC	1080	803-823
AV06822.um	GCAGCACAGUUACU GGACAAA	895	UUUGUCCAGUAAC UGUGCUGC	1081	823-843
AV06823.um	GAGCACAGUUACUG GACAACA	896	UGUUGUCCAGUAA CUGUGCUC	1082	824-844
AV06824.um	GGGACACAGCAGGA CACCAGA	897	UCUGGUGUCCUGC UGUGUCCC	1083	856-876
AV06825.um	CGACACCAGCAGCCC UUCCUA	898	UAGGAAGGGCUGC UGGUGUCG	1084	867-887
AV06826.um	GCCAGCAGCCCUUCC UAGAGA	899	UCUCUAGGAAGGG CUGCUGGC	1085	871-891
AV06827.um	GCAGCAGCCCUUCCU AGAGCA	900	UGCUCUAGGAAGG GCUGCUGC	1086	872-892
AV06828.um	CCAGCCCUUCCUAGA GCUUAA	901	UUAAGCUCUAGGA AGGGCUGG	1087	875-895
AV06829.um	GGAGCUUAAGAUCC GAGCCAA	902	UUGGCUCGGAUCU UAAGCUCC	1088	887-907
AV06830.um	GUCCGAGCCAAUGA GCCUGGA	903	UCCAGGCUCAUUG GCUCGGAC	1089	897-917
AV06831.um	GCGAGCCAAUGAGC CUGGAGA	904	UCUCCAGGCUCAU UGGCUCGC	1090	899-919
AV06832.um	GGAGCCAAUGAGCC UGGAGCA	905	UGCUCCAGGCUCA UUGGCUCC	1091	900-920
AV06833.um	GCCCCUUAUGUUGC AGGCGAA	906	UUCGCCUGCAACA UAAGGGGC	1092	961-981
AV06834.um	CACCAUUACGUAGA CUUCCAA	907	UUGGAAGUCUACG UAAUGGUG	1093	981-1001
AV06835.um	GUUCCAGGAACUGG GAUGGCA	908	UGCCAUCCCAGUU CCUGGAAC	1094	995-1015
AV06836.um	CAGGGGUACCAGCU GAAUUAA	909	UUAAUUCAGCUGG UACCCCUG	1095	1035-1055
AV06837.um	GCAGCUGAAUUACU GCAGUGA	910	UCACUGCAGUAAU UCAGCUGC	1096	1043-1063
AV06838.um	GGCUGAAUUACUGC AGUGGGA	911	UCCCACUGCAGUA AUUCAGCC	1097	1045-1065
AV06839.um	GAGCCCAGGCAUUG CUGCCUA	912	UAGGCAGCAAUGC CUGGGCUC	1098	1088-1108

AV06840.um	GCAGGCAUUGCUGCCUCUUUA	913	UAAAGAGGCAGCAAUGCCUGC	1099	1092-1112
AV06841.um	CCAUUGCUGCCUCUUUCCAUA	914	UAUGGAAAGAGGCAGCAAUGG	1100	1096-1116
AV06842.um	GUGCCUCUUUCCAUUCUGCCA	915	UGGCAGAAUGGAAAGAGGCAC	1101	1102-1122
AV06843.um	CCCUCUUUCCAUUCUGCCGUA	916	UACGGCAGAAUGGAAAGAGGG	1102	1104-1124
AV06844.um	GCUCUUUCCAUUCUGCCGUCA	917	UGACGGCAGAAUGGAAAGAGC	1103	1105-1125
AV06845.um	GUCUGCCGUCUUCAGCCUCCA	918	UGGAGGCUGAAGACGGCAGAC	1104	1115-1135
AV06846.um	GUUCAGCCUCCUCAAAGCCAA	919	UUGGCUUUGAGGAGGCUGAAC	1105	1124-1144
AV06847.um	GAAGCCAACAAUCCUUGGCCA	920	UGGCCAAGGAUUGUUGGCUUC	1106	1137-1157
AV06848.um	GGCCAACAAUCCUUGGCCUGA	921	UCAGGCCAAGGAUUGUUGGCC	1107	1139-1159
AV06849.um	GGUGUCCCUACUGCCCGAAGA	922	UCUUCGGGCAGUAGGGACACC	1108	1173-1193
AV06850.um	GCUCUCUCUCCUCUACCCUGGA	923	UCCAGGUAGAGGAGAGAGAGC	1109	1196-1216
AV06851.um	GUCUCUCUCCUCUACCUGGAA	924	UUCCAGGUAGAGGAGAGAGAC	1110	1197-1217
AV06852.um	GCUCUCUCCUCUACCUGGAUA	925	UAUCCAGGUAGAGGAGAGAGC	1111	1198-1218
AV06853.um	GCUCUCCUCUACCUGGAUCAA	926	UUGAUCCAGGUAGAGGAGAGC	1112	1200-1220
AV06854.um	GUCUACCUGGAUCAUAAUGGA	927	UCCAUUAUGAUCCAGGUAGAC	1113	1206-1226
AV06855.um	GACCUGGAUCAUAAUGGCAAA	928	UUUGCCAUUAUGAUCCAGGUC	1114	1209-1229
AV06856.um	GAUGUGGUCAAGACGGAUGUA	929	UACAUCCGUCUUGACCACAUC	1115	1227-1247
AV06857.um	GGUGGUCAAGACGGAUGUGCA	930	UGCACAUCCGUCUUGACCACC	1116	1229-1249
AV06858.um	CUCAAGACGGAUGUGCCAGAA	931	UUCUGGCACAUCCGUCUUGAG	1117	1233-1253
AV06859.um	GAGACGGAUGUGCCAGAUAUA	932	UAUAUCUGGCACAUCCGUCUC	1118	1236-1256
AV06860.um	GCGGAUGUGCCAGAUAUGGUA	933	UACCAUAUCUGGCACAUCCGC	1119	1239-1259
AV06861.um	CUGCCAGAUAUGGUGGUGGAA	934	UUCCACCACCAUAUCUGGCAG	1120	1245-1265
AV06862.um	CGGCUUUGGAGUGAAGAGACA	935	UGUCUCUUCACUCCAAAGCCG	1121	1296-1316
AV06863.um	CCUUUGGAGUGAAGAGACCAA	936	UUGGUCUCUUCACUCCAAAGG	1122	1298-1318
AV06864.um	GUUGGAGUGAAGAGACCAAGA	937	UCUUGGUCUCUUCACUCCAAC	1123	1300-1320
AV06865.um	GGGAGUGAAGAGACCAAGAUA	938	UAUCUUGGUCUCUUCACUCCC	1124	1302-1322
AV06866.um	CAGACCAAGAUGAAGUUUCCA	939	UGGAAACUUCAUCUUGGUCUG	1125	1311-1331
AV06867.um	GGACCAAGAUGAAGUUUCCCA	940	UGGGAAACUUCAUCUUGGUCC	1126	1312-1332
AV06868.um	GCAAGAUGAAGUUUCCCAGGA	941	UCCUGGGAAACUUCAUCUUGC	1127	1315-1335

AV06869.um	CAUGAAGUUUCCCA GGCACAA	942	UUGUGCCUGGGAA ACUUCAUG	1128	1319-1339
AV06870.um	CUUUCCCAGGCACA GGGCAUA	943	UAUGCCCUGUGCC UGGGAAAG	1129	1325-1345
AV06871.um	GUUCCCAGGCACAG GGCAUCA	944	UGAUGCCCUGUGC CUGGGAAC	1130	1326-1346
AV06872.um	GCCCAGGCACAGGG CAUCUGA	945	UCAGAUGCCCUGU GCCUGGGC	1131	1328-1348
AV06873.um	GGACUGGAGGCAUC AGAUUCA	946	UGAAUCUGAUGCC UCCAGUCC	1132	1348-1368
AV06874.um	GCUGGAGGCAUCAG AUUCCUA	947	UAGGAAUCUGAUG CCUCCAGC	1133	1350-1370
AV06875.um	GGGAGGCAUCAGAU UCCUGAA	948	UUCAGGAAUCUGA UGCCUCCC	1134	1352-1372
AV06876.um	CAUCCACACCCCAAC CCAACA	949	UGUUGGGUUGGGG UGUGGAUG	1135	1370-1390
AV06877.um	GCACCCCAACCCAAC AACCAA	950	UUGGUUGUUGGGU UGGGGUGC	1136	1375-1395
AV06878.um	GACCCCAACCCAACA ACCACA	951	UGUGGUUGUUGGG UUGGGGUC	1137	1376-1396
AV06879.um	GCAACCCAACAACCA CCUGGA	952	UCCAGGUGGUUGU UGGGUUGC	1138	1380-1400
AV06880.um	GACCCAACAACCACC UGGCAA	953	UUGCCAGGUGGUU GUUGGGUC	1139	1382-1402
AV06881.um	GCCCAACAACCACCU GGCAAA	954	UUUGCCAGGUGGU UGUUGGGC	1140	1383-1403
AV06882.um	GCCAACAACCACCUG GCAAUA	955	UAUUGCCAGGUGG UUGUUGGC	1141	1384-1404
AV06883.um	GAACCACCUGGCAA UAUGACA	956	UGUCAUAUUGCCA GGUGGUUC	1142	1389-1409
AV06884.um	GACCACCUGGCAAU AUGACUA	957	UAGUCAUAUUGCC AGGUGGUC	1143	1390-1410
AV06885.um	GCCACCUGGCAAUA UGACUCA	958	UGAGUCAUAUUGC CAGGUGGC	1144	1391-1411
AV06886.um	GCACCUGGCAAUAU GACUCAA	959	UUGAGUCAUAUUG CCAGGUGC	1145	1392-1412
AV06887.um	GACCUGGCAAUAUG ACUCACA	960	UGUGAGUCAUAUU GCCAGGUC	1146	1393-1413
AV06888.um	CCAAUAUGACUCAC UUGACCA	961	UGGUCAAGUGAGU CAUAUUGG	1147	1399-1419
AV06889.um	GUAUGACUCACUUG ACCCCUA	962	UAGGGGUCAAGUG AGUCAUAC	1148	1402-1422
AV06890.um	CACCCAAAUGGGCA CUUUCUA	963	UAGAAAGUGCCCA UUUGGGUG	1149	1426-1446
AV06891.um	GCCCAAAUGGGCAC UUUCUUA	964	UAAGAAAGUGCCC AUUUGGGC	1150	1427-1447
AV06892.um	GCCAAAUGGGCACU UUCUUGA	965	UCAAGAAAGUGCC CAUUUGGC	1151	1428-1448
AV06893.um	GGGGCACUUUCUUG UCUGAGA	966	UCUCAGACAAGAA AGUGCCCC	1152	1434-1454
AV06894.um	GAUUCCAGGUUGGC UGAUGUA	967	UACAUCAGCCAAC CUGGAAUC	1153	1463-1483
AV06895.um	GUUAGCCUCUCCCA AGAUGAA	968	UUCAUCUUGGGAG AGGCUAAC	1154	1607-1627
AV06896.um	GAGCCUCUCCCAAG AUGAGAA	969	UUCUCAUCUUGGG AGAGGCUC	1155	1609-1629
AV06897.um	GUCCCAAGAUGAGA AAGUCCA	970	UGGACUUUCUCAU CUUGGGAC	1156	1615-1635

AV06898.um	GCCCAAGAUGAGAAAGUCCUA	971	UAGGACUUUCUCAUCUUGGGC	1157	1616-1636
AV06899.um	GGGAGGAAGCAGAUAGAUGGA	972	UCCAUCUAUCUGCUUCCUCCC	1158	1647-1667
AV06900.um	CGAAGCAGAUAGAUGGUCCAA	973	UUGGACCAUCUAUCUGCUUCG	1159	1651-1671
AV06901.um	GAGCAGAUAGAUGGUCCAGCA	974	UGCUGGACCAUCUAUCUGCUC	1160	1653-1673
AV06902.um	GGCAGAUAGAUGGUCCAGCAA	975	UUGCUGGACCAUCUAUCUGCC	1161	1654-1674
AV06903.um	CAUGGUCCAGCAGGCUUGAAA	976	UUUCAAGCCUGCUGGACCAUG	1162	1662-1682
AV06904.um	CGCUUGAAGCAGGGUAAGCAA	977	UUGCUUACCCUGCUUCAAGCG	1163	1674-1694
AV06905.um	CGGAAGGUCAAGAGGGAGAUA	978	UAUCUCCCUCUUGACCUUCCG	1164	1730-1750
AV06906.um	CAAGGUCAAGAGGGAGAUGGA	979	UCCAUCUCCCUCUUGACCUUG	1165	1732-1752
AV06907.um	GCCCAGAAACAGGAGUCAGGA	980	UCCUGACUCCUGUUUCUGGGC	1166	1783-1803
AV06908.um	GCCAGAAACAGGAGUCAGGAA	981	UUCCUGACUCCUGUUUCUGGC	1167	1784-1804
AV06909.um	GCAGAAACAGGAGUCAGGAAA	982	UUUCCUGACUCCUGUUUCUGC	1168	1785-1805
AV06910.um	GGGCACUAAGCCUAAGAAGUA	983	UACUUCUUAGGCUUAGUGCCC	1169	1809-1829
AV06911.um	GAAGCCUAAGAAGUUCCCUGA	984	UCAGGGAACUUCUUAGGCUUC	1170	1815-1835
AV06912.um	GGCCUAAGAAGUUCCCUGGUA	985	UACCAGGGAACUUCUUAGGCC	1171	1817-1837
AV06913.um	GCUAAGAAGUUCCCUGGUUUA	986	UAAACCAGGGAACUUCUUAGC	1172	1819-1839
AV06914.um	GUAAGAAGUUCCCUGGUUUUA	987	UAAAACCAGGGAACUUCUUAC	1173	1820-1840
AV06915.um	GAAGAAGUUCCCUGGUUUUUA	988	UAAAAACCAGGGAACUUCUUC	1174	1821-1841
AV06916.um	GAGAAGUUCCCUGGUUUUUCA	989	UGAAAAACCAGGGAACUUCUC	1175	1822-1842
AV06917.um	GGAAGUUCCCUGGUUUUUCCA	990	UGGAAAAACCAGGGAACUUCC	1176	1823-1843
AV06918.um	CUUCCCUGGUUUUUCCCAGGA	991	UCCUGGGAAAAACCAGGGAAG	1177	1827-1847
AV06919.um	CGACAGGACCCACUGGGAGAA	992	UUCUCCCAGUGGGUCCUGUCG	1178	1847-1867
AV06920.um	CAGACAAGCAUUUAUACUUUA	993	UAAAGUAUAAAUGCUUGUCUG	1179	1863-1883
AV06921.um	GCUCUUGAUCCACCCGACUUA	994	UAAGUCGGGUGGAUCAAGAGC	1180	2103-2123
AV06922.um	GCGCGCCUGGCUUAUACUUUA	995	UAAAGUAUAAGCCAGGCGCGC	1181	2159-2179
AV06923.um	GGCGCCUGGCUUAUACUUUCA	996	UGAAAGUAUAAGCCAGGCGCC	1182	2160-2180
AV06924.um	CCGCCUGGCUUAUACUUUCUA	997	UAGAAAGUAUAAGCCAGGCGG	1183	2161-2181
AV06925.um	GCUGGCUUAUACUUUCUUAAA	998	UUUAAGAAAGUAUAAGCCAGC	1184	2164-2184
AV06926.um	GCUUUCUUAAUAAAAAGGAGA	999	UCUCCUUUUUAUUAAGAAAGC	1185	2174-2194

AV07024.um	GGACUCACUUGACCCCUAUGA	1000	UCAUAGGGGUCAAGUGAGUCC	1186	1405-1425
AV07025.um	CACUCACUUGACCCCUAUGGA	1001	UCCAUAGGGGUCAAGUGAGUG	1187	1406-1426
AV07026.um	CGACCCAAAUGGGCACUUUCA	1002	UGAAAGUGCCCAUUUGGGUCG	1188	1425-1445
AV07028.um	GACUUUCUUGUCUGAGACUCA	1003	UGAGUCUCAGACAAGAAAGUC	1189	1438-1458
AV07029.um	GUUCUUGUCUGAGACUCUGGA	1004	UCCAGAGUCUCAGACAAGAAC	1190	1441-1461
AV07030.um	GCUUGUCUGAGACUCUGGCUA	1005	UAGCCAGAGUCUCAGACAAGC	1191	1443-1463
AV07031.um	GUUGUCUGAGACUCUGGCUUA	1006	UAAGCCAGAGUCUCAGACAAC	1192	1444-1464
AV07032.um	GCCUGGUUUUUCCCAGGGGAA	1007	UUCCCCUGGGAAAAACCAGGC	1193	1830-1850
AV07033.um	GCUGGUUUUUCCCAGGGGACA	1008	UGUCCCCUGGGAAAAACCAGC	1194	1831-1851
AV07034.um	GUGGUUUUUCCCAGGGGACAA	1009	UUGUCCCCUGGGAAAAACCAC	1195	1832-1852
AV07035.um	GGGUUUUUCCCAGGGGACAGA	1010	UCUGUCCCCUGGGAAAAACCC	1196	1833-1853
AV07036.um	GUCCCAGGGGACAGGACCCAA	1011	UUGGGUCCUGUCCCCUGGGAC	1197	1839-1859
AV07037.um	GGGGGACAGGACCCACUGGGA	1012	UCCCAGUGGGUCCUGUCCCCC	1198	1844-1864
AV07038.um	CACAGGACCCACUGGGAGACA	1013	UGUCUCCCAGUGGGUCCUGUG	1199	1848-1868
AV07040.um	GGGACCCACUGGGAGACAAGA	1014	UCUUGUCUCCCAGUGGGUCCC	1200	1851-1871
AV07041.um	CACCCACUGGGAGACAAGCAA	1015	UUGCUUGUCUCCCAGUGGGUG	1201	1853-1873
AV07042.um	GCACUGGGAGACAAGCAUUUA	1016	UAAAUGCUUGUCUCCCAGUGC	1202	1856-1876
AV07043.um	GCUGGGAGACAAGCAUUUAUA	1017	UAUAAAUGCUUGUCUCCCAGC	1203	1858-1878
AV07044.um	GGGGAGACAAGCAUUUAUACA	1018	UGUAUAAAUGCUUGUCUCCCC	1204	1860-1880
AD02406-19.um	CUUUUCACCUGUCCACUCA	1019	UGAGUGGACAGGUGAAAAG	1205	559-577
AD02412-19.um	UUAAGAUCCGAGCCAAUGA	1020	UCAUUGGCUCGGAUCUUAA	1206	892-910
AD02413-19.um	UACGUAGACUUCCAGGAAA	1021	UUUCCUGGAAGUCUACGUA	1207	987-1005
AD02417-19.um	AUAUGACUCACUUGACCCA	1022	UGGGUCAAGUGAGUCAUAU	1208	1402-1420
AD02418-19.um	UGACUCACUUGACCCUAA	1023	UUAGGGGUCAAGUGAGUCA	1209	1405-1423
AD02423-19.um	CUAAGAAGUUCCCUGGUUA	1024	UAACCAGGGAACUUCUUAG	1210	1820-1838
AD02424-19.um	AAACGAGGUUUCAACAUGA	1025	UCAUGUUGAAACCUCGUUU	1211	2058-2076
AD02425-19.um	UAUACUUUCUUAAUAAAAA	1026	UUUUUAUUAAGAAAGUAUA	1212	2171-2189
AD02426-19.um	CUUUCUUAAUAAAAAGGAA	1027	UUCCUUUUUAUUAAGAAAG	1213	2175-2193
AD02427-19.um	CUUAAUAAAAAGGAGAAAA	1028	UUUUCUCCUUUUUAUUAAG	1214	2179-2197

AD02428-19.um	UUAAUAAAAAGGAGAAAGA	1029	UCUUUCUCCUUUUUAUUAA	1215	2180-2198
AD03263-19.um	CUACCUGGAUCAUAAUGGA	1030	UCCAUUAUGAUCCAGGUAG	1216	1208-1226
AD03243-19.um	CCUGGAUCAUAAUGGCAAA	1031	UUUGCCAUUAUGAUCCAGG	1217	1211-1229
AD03260-19.um	ACUGGAGGCAUCAGAUUCA	1032	UGAAUCUGAUGCCUCCAGU	1218	1350-1368
AD03250-19.um	GAGGCAUCAGAUUCCUGAA	1033	UUCAGGAAUCUGAUGCCUC	1219	1354-1372
AD03255-19.um	CCAAGAUGAGAAAGUCCUA	1034	UAGGACUUUCUCAUCUUGG	1220	1618-1636
AD03252-19.um	GACAAGCAUUUAUACUUUA	1035	UAAAGUAUAAAUGCUUGUC	1221	1865-1883
AD03238-19.um	UGUCUGAGACUCUGGCUUA	1036	UAAGCCAGAGUCUCAGACA	1222	1446-1464

【0116】 表2示出了本發明的某些經化學修飾的INHBE RNAi藥劑反義鏈序列和有義鏈序列。在本發明的方法的一些實施方案中，將具有表2所示的多核苷酸序列的RNAi藥劑施用於細胞和/或受試者。在本發明的方法的一些實施方案中，將具有表2所示的多核苷酸序列的RNAi藥劑施用於受試者。在本發明的一些實施方案中，施用於受試者的RNAi藥劑包含表2第一列的某一行中標識的雙鏈體，並且包含表2第三列和第六列的同一行中的有義鏈序列和反義鏈序列分別所示的序列修飾。在本發明的方法的一些實施方案中，表2所示的序列可與能夠將RNAi藥劑遞送至受試者體內的細胞和/或組織的化合物連接（本文也稱為“綴合”）。可用於本發明的某些實施方案的遞送化合物的非限制性示例是含GalNAc的化合物或含GLS-15*的化合物。在表2中，第一列表示具有如表1所示的鹼基序列的雙鏈體AV#。表2公開了雙鏈體AV#，並且還示出了包含在雙鏈體的有義序列和反義序列中的化學修飾。例如，表1示出了鹼基單鏈序列SEQ ID NO: 23（有義）和SEQ ID NO: 275（反義），它們一起形成標識為以下項的雙鏈的雙鏈體：雙鏈體AV# AV01605.um，並且表2列出了雙鏈體AV# AV01605，其表明

SEQ ID NO: 527和SEQ ID NO: 653的雙鏈體分別包含SEQ ID NO: 23和SEQ ID NO: 275的鹼基序列，但具有分別示於第三列和第六列中的有義序列和反義序列所示的化學修飾。表2第二列中的“有義鏈SS#”是同一行中第3列所示的有義序列（包括修飾）的所分配的標識符。表2第五列中的“反義鏈AS#”是第六列所示的反義序列（包括修飾）的所分配的標識符。

【0117】 表2：提供了經化學修飾的INHBE RNAi藥劑反義鏈序列和有義鏈序列。所有序列均以5'至3'示出。這些序列用於本文所述的某些體外測試研究。

雙鏈體AV#	有義鏈SS#	有義序列	SEQ ID NO.	反義鏈AS#	反義序列	SEQ ID NO.
AV01591	AV01591-SS	c*g*ugcuggAfgCfuAfgccaag*c*a	513	AV01591-AS	u*Gf*cuUfg(gUNA)cuagCfuCfcAfgca*c*g	639
AV01592	AV01592-SS	g*u*agccaaGfcAfgCfaaaucc*u*a	514	AV01592-AS	u*Af*ggauUfugcuGfcUfuGfgcu*a*c	640
AV01593	AV01593-SS	g*c*agucguCfcCfaGfaauaac*u*a	515	AV01593-AS	u*Af*guuaUfucugGfgAfcGfacu*g*c	641
AV01594	AV01594-SS	g*c*agacucCfaCfuUfcagccu*a*a	516	AV01594-AS	u*Uf*agGfc(uUNA)gaagUfgGfaGfucu*g*c	642
AV01595	AV01595-SS	g*a*gacuccAfcUfuCfagccua*c*a	517	AV01595-AS	u*Gf*uaGfg(cUNA)ugaaGfuGfgAfguc*u*c	643
AV01596	AV01596-SS	g*u*uuucacCfuGfuCfcacucc*u*a	518	AV01596-AS	u*Af*ggAfg(uUNA)ggacAfgGfuGfaaa*a*c	644
AV01597	AV01597-SS	c*u*cccaccAfcCfuGfuaccau*g*a	519	AV01597-AS	u*Cf*auggUfacagGfuGfgUfggg*a*g	645
AV01598	AV01598-SS	g*c*cacccuUfcCfuGfgcacuc*u*a	520	AV01598-AS	u*Af*gaGfu(gUNA)ccagGfaAfgGfgug*g*c	646
AV01599	AV01599-SS	g*u*uccuggCfaCfuCfuuugcu*u*a	521	AV01599-AS	u*Af*agcaAfagagUfgCfcAfgga*a*c	647
AV01600	AV01600-SS	g*c*cuggcaCfuCfuUfugcuug*a*a	522	AV01600-AS	u*Uf*caagCfaaagAfgUfgCfcag*g*c	648
AV01601	AV01601-SS	g*c*uggcacUfcUfuUfgcuuga*g*a	523	AV01601-AS	u*Cf*ucAfa(gUNA)caaaGfaGfuGfcca*g*c	649
AV01602	AV01602-SS	g*u*ggcacuCfuUfuGfcuugag*g*a	524	AV01602-AS	u*Cf*cuCfa(aUNA)gcaaAfgAfgUfgcc*a*c	650
AV01603	AV01603-SS	c*g*cacucuUfuGfcUfugagga*u*a	525	AV01603-AS	u*Af*uccuCfaagcAfaAfgAfgug*c*g	651
AV01604	AV01604-SS	c*c*acucuuUfgCfuUfgaggau*c*a	526	AV01604-AS	u*Gf*auCfc(uUNA)caagCfaAfaGfagu*g*g	652
AV01605	AV01605-SS	g*a*cucuuuGfcUfuGfaggauc*u*a	527	AV01605-AS	u*Af*gaucCfucaaGfcAfaAfgag*u*c	653
AV01606	AV01606-SS	g*u*gcuugaGfgAfuCfuuccga*u*a	528	AV01606-AS	u*Af*ucggAfagauCfcUfcAfagc*a*c	654
AV01607	AV01607-SS	g*u*gcccucUfaGfuGfgcuuga*g*a	529	AV01607-AS	u*Cf*ucAfa(gUNA)ccacUfaGfaGfggc*a*c	655

AV01608	AV01608-SS	c*g*ggugagAfaGfuCfuggugu*c*a	530	AV01608-AS	u*Gf*acAfc(cUNA)agacUfuCfuCfacc*c*g	656
AV01609	AV01609-SS	c*g*ugagaaGfuCfuGfgugucc*u*a	531	AV01609-AS	u*Af*ggAfc(aUNA)ccagAfcUfuCfuca*c*g	657
AV01610	AV01610-SS	c*a*gaagucUfgGfuGfuccuga*a*a	532	AV01610-AS	u*Uf*ucagGfacacCfaGfaCfuuc*u*g	658
AV01611	AV01611-SS	c*a*agucugGfuGfuCfcugaaa*c*a	533	AV01611-AS	u*Gf*uuucAfggacAfcCfaGfacu*u*g	659
AV01612	AV01612-SS	g*a*gucuggUfgUfcCfugaaac*u*a	534	AV01612-AS	u*Af*guuuCfaggaCfaCfcAfgac*u*c	660
AV01613	AV01613-SS	c*g*uguccuGfaAfaCfugcaac*u*a	535	AV01613-AS	u*Af*guugCfaguuUfcAfgGfaca*c*g	661
AV01614	AV01614-SS	c*u*guccugAfaAfcUfgcaacu*a*a	536	AV01614-AS	u*Uf*aguuGfcaguUfuCfaGfgac*a*g	662
AV01615	AV01615-SS	g*g*uccugaAfaCfuGfcaacua*g*a	537	AV01615-AS	u*Cf*uaguUfgcagUfuUfcAfgga*c*c	663
AV01616	AV01616-SS	c*u*ccugaaAfcUfgCfaacuag*a*a	538	AV01616-AS	u*Uf*cuagUfugcaGfuUfuCfagg*a*g	664
AV01617	AV01617-SS	g*c*cugaaaCfuGfcAfacuaga*c*a	539	AV01617-AS	u*Gf*ucuaGfuugcAfgUfuUfcag*g*c	665
AV01618	AV01618-SS	g*c*ugaaacUfgCfaAfcuagac*u*a	540	AV01618-AS	u*Af*gucuAfguugCfaGfuUfuca*g*c	666
AV01619	AV01619-SS	c*a*aacugcAfaCfuAfgacugc*a*a	541	AV01619-AS	u*Uf*gcAfg(uUNA)cuagUfuGfcAfguu*u*g	667
AV01620	AV01620-SS	g*a*cugcaaCfuAfgAfcugcag*a*a	542	AV01620-AS	u*Uf*cuGfc(aUNA)gucuAfgUfuGfcag*u*c	668
AV01621	AV01621-SS	g*a*cagcacAfgUfuAfcuggac*a*a	543	AV01621-AS	u*Uf*guCfc(aUNA)guaaCfuGfuGfcug*u*c	669
AV01622	AV01622-SS	g*c*uuccuaGfaGfcUfuaagau*c*a	544	AV01622-AS	u*Gf*aucuUfaagcUfcUfaGfgaa*g*c	670
AV01623	AV01623-SS	g*u*uccuagAfgCfuUfaagauc*c*a	545	AV01623-AS	u*Gf*gaucUfuaagCfuCfuAfgga*a*c	671
AV01624	AV01624-SS	c*a*gcuuaaGfaUfcCfgagcca*a*a	546	AV01624-AS	u*Uf*ugGfc(uUNA)cggaUfcUfuAfagc*u*g	672
AV01625	AV01625-SS	g*g*cuuaagAfuCfcGfagccaa*u*a	547	AV01625-AS	u*Af*uuggCfucggAfuCfuUfaag*c*c	673
AV01626	AV01626-SS	g*u*gcgaccCfcCfuUfauguug*c*a	548	AV01626-AS	u*Gf*caacAfuaagGfgGfgUfcgc*a*c	674
AV01627	AV01627-SS	g*g*cgacccCfcUfuAfuguugc*a*a	549	AV01627-AS	u*Uf*gcaaCfauaaGfgGfgGfucg*c*c	675
AV01628	AV01628-SS	c*a*gaccauUfaCfgUfagacuu*c*a	550	AV01628-AS	u*Gf*aaguCfuacgUfaAfuGfguc*u*g	676
AV01629	AV01629-SS	g*g*accauuAfcGfuAfgacuuc*c*a	551	AV01629-AS	u*Gf*gaAfg(uUNA)cuacGfuAfaUfggu*c*c	677
AV01630	AV01630-SS	g*u*acguagAfcUfuCfcaggaa*c*a	552	AV01630-AS	u*Gf*uuCfc(uUNA)ggaaGfuCfuAfcgu*a*c	678
AV01631	AV01631-SS	g*a*cguagaCfuUfcCfaggaac*u*a	553	AV01631-AS	u*Af*guucCfuggaAfgUfcUfacg*u*c	679
AV01632	AV01632-SS	c*g*gguaccAfgCfuGfaauuac*u*a	554	AV01632-AS	u*Af*guaaUfucagCfuGfgUfacc*c*g	680
AV01633	AV01633-SS	c*u*accagcUfgAfaUfuacugc*a*a	555	AV01633-AS	u*Uf*gcagUfaauuCfaGfcUfggu*a*g	681
AV01634	AV01634-SS	g*a*uugcugCfcUfcUfuuccau*u*a	556	AV01634-AS	u*Af*auggAfaagaGfgCfaGfcaa*u*c	682
AV01635	AV01635-SS	g*u*ugcugcCfuCfuUfuccauu*c*a	557	AV01635-AS	u*Gf*aaugGfaaagAfgGfcAfgca*a*c	683
AV01636	AV01636-SS	g*u*gcugccUfcUfuUfccauuc*u*a	558	AV01636-AS	u*Af*gaauGfgaaaGfaGfgCfagc*a*c	684

AV01637	AV01637-SS	g*g*cugccuCfuUfuCfcauucu*g*a	559	AV01637-AS	u*Cf*agaaUfggaaAfgAfgGfcag*c*c	685
AV01638	AV01638-SS	g*c*uuuccaUfuCfuGfccgucu*u*a	560	AV01638-AS	u*Af*agAfc(gUNA)gcagAfaUfgGfaaa*g*c	686
AV01639	AV01639-SS	g*g*ucuucaGfcCfuCfcucaaa*g*a	561	AV01639-AS	u*Cf*uuugAfggagGfcUfgAfaga*c*c	687
AV01640	AV01640-SS	g*u*ccucaaAfgCfcAfacaauc*c*a	562	AV01640-AS	u*Gf*gauuGfuuggCfuUfuGfagg*a*c	688
AV01641	AV01641-SS	g*c*cucaaaGfcCfaAfcaaucc*u*a	563	AV01641-AS	u*Af*ggauUfguugGfcUfuUfgag*g*c	689
AV01642	AV01642-SS	g*a*uccuugGfcCfuGfccagua*c*a	564	AV01642-AS	u*Gf*uaCfu(gUNA)gcagGfcCfaAfgga*u*c	690
AV01643	AV01643-SS	g*u*cuccucUfaCfcUfggauca*u*a	565	AV01643-AS	u*Af*ugauCfcaggUfaGfaGfgag*a*c	691
AV01644	AV01644-SS	g*c*uccucuAfcCfuGfgaucau*a*a	566	AV01644-AS	u*Uf*augaUfccagGfuAfgAfgga*g*c	692
AV01645	AV01645-SS	g*u*ccucuaCfcUfgGfaucaua*a*a	567	AV01645-AS	u*Uf*uaugAfuccaGfgUfaGfagg*a*c	693
AV01646	AV01646-SS	g*c*ucuaccUfgGfaUfcauaau*g*a	568	AV01646-AS	u*Cf*auuaUfgaucCfaGfgUfaga*g*c	694
AV01647	AV01647-SS	g*u*ggaucaUfaAfuGfgcaaug*u*a	569	AV01647-AS	u*Af*cauuGfccauUfaUfgAfucc*a*c	695
AV01648	AV01648-SS	g*g*gaucauAfaUfgGfcaaugu*g*a	570	AV01648-AS	u*Cf*acauUfgccaUfuAfuGfauc*c*c	696
AV01649	AV01649-SS	c*g*aucauaAfuGfgCfaaugug*g*a	571	AV01649-AS	u*Cf*cacaUfugccAfuUfaUfgau*c*g	697
AV01650	AV01650-SS	g*a*uaauggCfaAfuGfugguca*a*a	572	AV01650-AS	u*Uf*ugacCfacauUfgCfcAfuua*u*c	698
AV01651	AV01651-SS	g*a*auggcaAfuGfuGfgucaag*a*a	573	AV01651-AS	u*Uf*cuugAfccacAfuUfgCfcau*u*c	699
AV01652	AV01652-SS	g*a*agacggAfuGfuGfccagau*a*a	574	AV01652-AS	u*Uf*aucuGfgcacAfuCfcGfucu*u*c	700
AV01653	AV01653-SS	c*a*ugugccAfgAfuAfuggugg*u*a	575	AV01653-AS	u*Af*ccAfc(cUNA)auauCfuGfgCfaca*u*g	701
AV01654	AV01654-SS	c*u*ggcugcAfgCfuAfgcaaga*g*a	576	AV01654-AS	u*Cf*ucUfu(gUNA)cuagCfuGfcAfgcc*a*g	702
AV01655	AV01655-SS	c*c*aagaggAfcCfuGfggcuu*u*a	577	AV01655-AS	u*Af*aaGfc(cUNA)ccagGfuCfcUfcuu*g*g	703
AV01656	AV01656-SS	g*u*ggagugAfaGfaGfaccaag*a*a	578	AV01656-AS	u*Uf*cuugGfucucUfuCfaCfucc*a*c	704
AV01657	AV01657-SS	c*g*agugaaGfaGfaCfcaagau*g*a	579	AV01657-AS	u*Cf*aucuUfggucUfcUfuCfacu*c*g	705
AV01658	AV01658-SS	c*a*gugaagAfgAfcCfaagaug*a*a	580	AV01658-AS	u*Uf*caucUfugguCfuCfuUfcac*u*g	706
AV01659	AV01659-SS	g*g*aagagaCfcAfaGfaugaag*u*a	581	AV01659-AS	u*Af*cuucAfucuuGfgUfcUfcuu*c*c	707
AV01660	AV01660-SS	g*a*gagaccAfaGfaUfgaaguu*u*a	582	AV01660-AS	u*Af*aacuUfcaucUfuGfgUfcuc*u*c	708
AV01661	AV01661-SS	g*g*agaccaAfgAfuGfaaguuu*c*a	583	AV01661-AS	u*Gf*aaacUfucauCfuUfgGfucu*c*c	709
AV01662	AV01662-SS	c*a*ccaagaUfgAfaGfuuuccc*a*a	584	AV01662-AS	u*Uf*gggaAfacuuCfaUfcUfugg*u*g	710
AV01663	AV01663-SS	c*a*cuggagGfcAfuCfagauuc*c*a	585	AV01663-AS	u*Gf*gaauCfugauGfcCfuCfcag*u*g	711
AV01664	AV01664-SS	g*a*acaaccAfcCfuGfgcaaua*u*a	586	AV01664-AS	u*Af*uauuGfccagGfuGfgUfugu*u*c	712
AV01665	AV01665-SS	g*a*caaccaCfcUfgGfcaauau*g*a	587	AV01665-AS	u*Cf*auauUfgccaGfgUfgGfuug*u*c	713

AV01666	AV01666-SS	g*c*aaccacCfuGfgCfaauaug*a*a	588	AV01666-AS	u*Uf*cauaUfugccAfgGfuGfguu*g*c	714
AV01667	AV01667-SS	g*c*cuggcaAfuAfuGfacucac*u*a	589	AV01667-AS	u*Af*gugaGfucauAfuUfgCfcag*g*c	715
AV01668	AV01668-SS	g*c*uggcaaUfaUfgAfcucacu*u*a	590	AV01668-AS	u*Af*agugAfgucaUfaUfuGfcca*g*c	716
AV01669	AV01669-SS	g*u*ggcaauAfuGfaCfucacuu*g*a	591	AV01669-AS	u*Cf*aaguGfagucAfuAfuUfgcc*a*c	717
AV01670	AV01670-SS	c*g*caauauGfaCfuCfacuuga*c*a	592	AV01670-AS	u*Gf*ucaaGfugagUfcAfuAfuug*c*g	718
AV01671	AV01671-SS	g*u*gacucaCfuUfgAfccccua*u*a	593	AV01671-AS	u*Af*uaGfg(gUNA)gucaAfgUfgAfguc*a*c	719
AV01672	AV01672-SS	g*c*aaauggGfcAfcUfuucuug*u*a	594	AV01672-AS	u*Af*caagAfaaguGfcCfcAfuuu*g*c	720
AV01673	AV01673-SS	g*a*aaugggCfaCfuUfucuugu*c*a	595	AV01673-AS	u*Gf*acaaGfaaagUfgCfcCfauu*u*c	721
AV01674	AV01674-SS	g*a*augggcAfcUfuUfcuuguc*u*a	596	AV01674-AS	u*Af*gacaAfgaaaGfuGfcCfcau*u*c	722
AV01675	AV01675-SS	g*a*ugggcaCfuUfuCfuugucu*g*a	597	AV01675-AS	u*Cf*agacAfagaaAfgUfgCfcca*u*c	723
AV01676	AV01676-SS	g*u*gggcacUfuUfcUfugucug*a*a	598	AV01676-AS	u*Uf*cagaCfaagaAfaGfuGfccc*a*c	724
AV01677	AV01677-SS	c*g*gcacuuUfcUfuGfucugag*a*a	599	AV01677-AS	u*Uf*cucaGfacaaGfaAfaGfugc*c*g	725
AV01678	AV01678-SS	c*g*cacuuuCfuUfgUfcugaga*c*a	600	AV01678-AS	u*Gf*ucUfc(aUNA)gacaAfgAfaAfgug*c*g	726
AV01679	AV01679-SS	c*c*acuuucUfuGfuCfugagac*u*a	601	AV01679-AS	u*Af*gucuCfagacAfaGfaAfagu*g*g	727
AV01680	AV01680-SS	g*c*uuucuuGfuCfuGfagacuc*u*a	602	AV01680-AS	u*Af*gaguCfucagAfcAfaGfaaa*g*c	728
AV01681	AV01681-SS	g*u*auuccaGfgUfuGfgcugau*g*a	603	AV01681-AS	u*Cf*auCfa(gUNA)ccaaCfcUfgGfaau*a*c	729
AV01682	AV01682-SS	g*c*cagguuGfgCfuGfaugugu*u*a	604	AV01682-AS	u*Af*acacAfucagCfcAfaCfcug*g*c	730
AV01683	AV01683-SS	c*u*uucuucUfaAfaGfgggucu*a*a	605	AV01683-AS	u*Uf*agAfc(cUNA)ccuuUfaGfaAfgaa*a*g	731
AV01684	AV01684-SS	g*a*cuuagcCfuCfuCfccaaga*u*a	606	AV01684-AS	u*Af*ucuuGfggagAfgGfcUfaag*u*c	732
AV01685	AV01685-SS	g*c*ucucccAfaGfaUfgagaaa*g*a	607	AV01685-AS	u*Cf*uuucUfcaucUfuGfgGfaga*g*c	733
AV01686	AV01686-SS	g*u*cucccaAfgAfuGfagaaag*u*a	608	AV01686-AS	u*Af*cuuuCfucauCfuUfgGfgag*a*c	734
AV01687	AV01687-SS	g*c*ucccaaGfaUfgAfgaaagu*c*a	609	AV01687-AS	u*Gf*acuuUfcucaUfcUfuGfgga*g*c	735
AV01688	AV01688-SS	c*a*ggaggaAfgCfaGfauagau*g*a	610	AV01688-AS	u*Cf*aucuAfucugCfuUfcCfucc*u*g	736
AV01689	AV01689-SS	c*g*aggaagCfaGfaUfagaugg*u*a	611	AV01689-AS	u*Af*ccauCfuaucUfgCfuUfccu*c*g	737
AV01690	AV01690-SS	c*a*ggaagcAfgAfuAfgauggu*c*a	612	AV01690-AS	u*Gf*acCfa(uUNA)cuauCfuGfcUfucc*u*g	738
AV01691	AV01691-SS	c*u*ccagcaGfgCfuUfgaagca*g*a	613	AV01691-AS	u*Cf*ugCfu(uUNA)caagCfcUfgCfugg*a*g	739
AV01692	AV01692-SS	g*a*gaaacaGfgAfgUfcaggaa*a*a	614	AV01692-AS	u*Uf*uuccUfgacuCfcUfgUfuuc*u*c	740
AV01693	AV01693-SS	c*a*ggcacuAfaGfcCfuaagaa*g*a	615	AV01693-AS	u*Cf*uucuUfaggcUfuAfgUfgcc*u*g	741
AV01694	AV01694-SS	c*g*cacuaaGfcCfuAfagaagu*u*a	616	AV01694-AS	u*Af*acuuCfuuagGfcUfuAfgug*c*g	742

AV01695	AV01695-SS	c*c*acuaagCfcUfaAfgaaguu*c*a	617	AV01695-AS	u*Gf*aacuUfcuuaGfgCfuUfagu*g*g	743
AV01696	AV01696-SS	g*c*aggaccCfaCfuGfggagac*a*a	618	AV01696-AS	u*Uf*guCfu(cUNA)ccagUfgGfgUfccu*g*c	744
AV01697	AV01697-SS	g*a*cugggaGfaCfaAfgcauuu*a*a	619	AV01697-AS	u*Uf*aaauGfcuugUfcUfcCfcag*u*c	745
AV01698	AV01698-SS	c*g*gagacaAfgCfaUfuuauac*u*a	620	AV01698-AS	u*Af*guauAfaaugCfuUfgUfcuc*c*g	746
AV01699	AV01699-SS	c*g*agacaaGfcAfuUfuauacu*u*a	621	AV01699-AS	u*Af*aguaUfaaauGfcUfuGfucu*c*g	747
AV01700	AV01700-SS	g*g*acaagcAfuUfuAfuacuuu*c*a	622	AV01700-AS	u*Gf*aaagUfauaaAfuGfcUfugu*c*c	748
AV01701	AV01701-SS	c*a*caagcaUfuUfaUfacuuuc*u*a	623	AV01701-AS	u*Af*gaaaGfuauaAfaUfgCfuug*u*g	749
AV01702	AV01702-SS	g*c*aagcauUfuAfuAfcuuucu*u*a	624	AV01702-AS	u*Af*agaaAfguauAfaAfuGfcuu*g*c	750
AV01703	AV01703-SS	g*a*ggcgccCfaCfuAfauuuuu*g*a	625	AV01703-AS	u*Cf*aaaaAfuuagUfgGfgCfgcc*u*c	751
AV01704	AV01704-SS	g*g*ccuggcUfuAfuAfcuuucu*u*a	626	AV01704-AS	u*Af*agaaAfguauAfaGfcCfagg*c*c	752
AV01705	AV01705-SS	c*c*cuggcuUfaUfaCfuuucuu*a*a	627	AV01705-AS	u*Uf*aagaAfaguaUfaAfgCfcag*g*g	753
AV01706	AV01706-SS	g*u*ggcuuaUfaCfuUfucuuaa*u*a	628	AV01706-AS	u*Af*uuaaGfaaagUfaUfaAfgcc*a*c	754
AV01707	AV01707-SS	g*g*gcuuauAfcUfuUfcuuaau*a*a	629	AV01707-AS	u*Uf*auuaAfgaaaGfuAfuAfagc*c*c	755
AV01708	AV01708-SS	c*g*cuuauaCfuUfuCfuuaaua*a*a	630	AV01708-AS	u*Uf*uauuAfagaaAfgUfaUfaag*c*g	756
AV01709	AV01709-SS	g*u*uucuuaAfuAfaAfaaggag*a*a	631	AV01709-AS	u*Uf*cuccUfuuuuAfuUfaAfgaa*a*c	757
AV01710	AV01710-SS	g*u*ucuuaaUfaAfaAfaggaga*a*a	632	AV01710-AS	u*Uf*ucucCfuuuuUfaUfuAfaga*a*c	758
AV03974	AV03974-SS	c*a*agcauuUfaUfaCfuuucuu*u*u	633	AV03974-AS	a*Af*aagaAfaguaUfaAfaUfgcu*u*g	759
AV03975	AV03975-SS	c*c*agucguCfcCfaGfaauaac*u*u	634	AV03975-AS	a*Af*guuaUfucugGfgAfcGfacu*g*g	760
AV03976	AV03976-SS	a*c*agacggAfgCfaAfcugcca*u*u	635	AV03976-AS	a*Af*uggcAfguugCfuCfcGfucu*g*u	761
AV03977	AV03977-SS	u*c*ccagaaUfaAfcUfcauccu*c*u	636	AV03977-AS	a*Gf*aggaUfgaguUfaUfuCfugg*g*a	762
AV03978	AV03978-SS	c*c*agguugGfcUfgAfuguguu*g*u	637	AV03978-AS	a*Cf*aacaCfaucaGfcCfaAfccu*g*g	763
AV03979	AV03979-SS	g*a*uuuccuGfcCfcUfaagucc*u*u	638	AV03979-AS	a*Af*ggacUfuaggGfcAfgGfaaa*u*c	764
AV05265	AV05265-SS	g*a*cuuuucAfcCfuGfuccacu*c*a	1223	AV05265-AS	u*Gf*agUfg(gUNA)acagGfuGfaAfaag*u*c	1524
AV05266	AV05266-SS	g*u*uuucacCfuGfuCfcacucc*u*a	1224	AV05266-AS	u*Af*ggAfg(uUNA)ggacAfgGfuGfaaa*a*c	1525
AV05267	AV05267-SS	c*u*cccaccAfcCfuGfuaccau*g*a	1225	AV05267-AS	u*Cf*auggUfacagGfuGfgUfggg*a*g	1526
AV05268	AV05268-SS	g*c*cacccuUfcCfuGfgcacuc*u*a	1226	AV05268-AS	u*Af*gaGfu(gUNA)ccagGfaAfgGfgug*g*c	1527
AV05269	AV05269-SS	g*a*cucuuuGfcUfuGfaggauc*u*a	1227	AV05269-AS	u*Af*gaucCfucaaGfcAfaAfgag*u*c	1528
AV05270	AV05270-SS	g*c*ucugccCfuCfuAfguggcu*u*a	1228	AV05270-AS	u*Af*agCfc(aUNA)cuagAfgGfgCfaga*g*c	1529
AV05271	AV05271-SS	g*u*gcccucUfaGfuGfgcuuga*g*a	1229	AV05271-AS	u*Cf*ucAfa(gUNA)ccacUfaGfaGfggc*a*c	1530

AV05272	AV05272-SS	c*g*ggugagAfaGfuCfuggugu*c*a	1230	AV05272-AS	u*Gf*acAfc(cUNA)agacUfuCfuCfacc*c*g	1531
AV05273	AV05273-SS	c*g*ugagaaGfuCfuGfgugucc*u*a	1231	AV05273-AS	u*Af*ggAfc(aUNA)ccagAfcUfuCfuca*c*g	1532
AV05274	AV05274-SS	c*a*gaagucUfgGfuGfuccuga*a*a	1232	AV05274-AS	u*Uf*ucagGfacacCfaGfaCfuuc*u*g	1533
AV05275	AV05275-SS	c*a*agucugGfuGfuCfcugaaa*c*a	1233	AV05275-AS	u*Gf*uuucAfggacAfcCfaGfacu*u*g	1534
AV05276	AV05276-SS	g*u*uccuagAfgCfuUfaagauc*c*a	1234	AV05276-AS	u*Gf*gaucUfuaagCfuCfuAfgga*a*c	1535
AV05277	AV05277-SS	c*a*gcuuaaGfaUfcCfgagcca*a*a	1235	AV05277-AS	u*Uf*ugGfc(uUNA)cggaUfcUfuAfagc*u*g	1536
AV05278	AV05278-SS	g*g*cuuaagAfuCfcGfagccaa*u*a	1236	AV05278-AS	u*Af*uuggCfucggAfuCfuUfaag*c*c	1537
AV05279	AV05279-SS	c*c*uuaagaUfcCfgAfgccaau*g*a	1237	AV05279-AS	u*Cf*auUfg(gUNA)cucgGfaUfcUfuaa*g*g	1538
AV05280	AV05280-SS	c*g*acccccAfcCfuGfugagcc*u*a	1238	AV05280-AS	u*Af*ggCfu(cUNA)acagGfuGfgGfggu*c*g	1539
AV05281	AV05281-SS	g*u*gcgaccCfcCfuUfauguug*c*a	1239	AV05281-AS	u*Gf*caacAfuaagGfgGfgUfcgc*a*c	1540
AV05282	AV05282-SS	g*g*cgacccCfcUfuAfuguugc*a*a	1240	AV05282-AS	u*Uf*gcaaCfauaaGfgGfgGfucg*c*c	1541
AV05283	AV05283-SS	g*g*acccccUfuAfuGfuugcag*g*a	1241	AV05283-AS	u*Cf*cuGfc(aUNA)acauAfaGfgGfggu*c*c	1542
AV05284	AV05284-SS	c*a*gaccauUfaCfgUfagacuu*c*a	1242	AV05284-AS	u*Gf*aaguCfuacgUfaAfuGfguc*u*g	1543
AV05285	AV05285-SS	g*g*accauuAfcGfuAfgacuuc*c*a	1243	AV05285-AS	u*Gf*gaAfg(uUNA)cuacGfuAfaUfggu*c*c	1544
AV05286	AV05286-SS	g*u*uacguaGfaCfuUfccagga*a*a	1244	AV05286-AS	u*Uf*ucCfu(gUNA)gaagUfcUfaCfgua*a*c	1545
AV05287	AV05287-SS	c*g*gguaccAfgCfuGfaauuac*u*a	1245	AV05287-AS	u*Af*guaaUfucagCfuGfgUfacc*c*g	1546
AV05288	AV05288-SS	g*a*uccuugGfcCfuGfccagua*c*a	1246	AV05288-AS	u*Gf*uaCfu(gUNA)gcagGfcCfaAfgga*u*c	1547
AV05289	AV05289-SS	c*c*aagaggAfcCfuGfggcuu*u*a	1247	AV05289-AS	u*Af*aaGfc(cUNA)ccagGfuCfcUfcuu*g*g	1548
AV05290	AV05290-SS	c*g*accuggGfgCfuUfuggagu*g*a	1248	AV05290-AS	u*Cf*acUfc(cUNA)aaagCfcCfcAfggu*c*g	1549
AV05291	AV05291-SS	c*a*ccugggGfcUfuUfggagug*a*a	1249	AV05291-AS	u*Uf*caCfu(cUNA)caaaGfcCfcCfagg*u*g	1550
AV05292	AV05292-SS	g*u*ggagugAfaGfaGfaccaag*a*a	1250	AV05292-AS	u*Uf*cuugGfucucUfuCfaCfucc*a*c	1551
AV05293	AV05293-SS	c*a*cuggagGfcAfuCfagauuc*c*a	1251	AV05293-AS	u*Gf*gaauCfugauGfcCfuCfcag*u*g	1552
AV05294	AV05294-SS	g*a*auaugaCfuCfaCfuugacc*c*a	1252	AV05294-AS	u*Gf*ggUfc(aUNA)agugAfgUfcAfuau*u*c	1553
AV05295	AV05295-SS	g*a*ugacucAfcUfuGfaccccu*a*a	1253	AV05295-AS	u*Uf*agGfg(gUNA)ucaaGfuGfaGfuca*u*c	1554
AV05296	AV05296-SS	g*u*gacucaCfuUfgAfccccua*u*a	1254	AV05296-AS	u*Af*uaGfg(gUNA)gucaAfgUfgAfguc*a*c	1555
AV05297	AV05297-SS	g*u*auuccaGfgUfuGfgcugau*g*a	1255	AV05297-AS	u*Cf*auCfa(gUNA)ccaaCfcUfgGfaau*a*c	1556
AV05298	AV05298-SS	c*u*uucuucUfaAfaGfggucu*a*a	1256	AV05298-AS	u*Uf*agAfc(cUNA)ccuuUfaGfaAfgaa*a*g	1557
AV05299	AV05299-SS	g*a*cuuagcCfuCfuCfccaaga*u*a	1257	AV05299-AS	u*Af*ucuuGfggagAfgGfcUfaag*u*c	1558
AV05300	AV05300-SS	g*c*ucucccAfaGfaUfgagaaa*g*a	1258	AV05300-AS	u*Cf*uuucUfcaucUfuGfgGfaga*g*c	1559

AV05301	AV05301-SS	g*u*cucccaAfgAfuGfagaaag*u*a	1259	AV05301-AS	u*Af*cuuuCfucauCfuUfgGfgag*a*c	1560
AV05302	AV05302-SS	g*c*ucccaaGfaUfgAfgaaagu*c*a	1260	AV05302-AS	u*Gf*acuuUfcucaUfcUfuGfgga*g*c	1561
AV05303	AV05303-SS	g*a*gaaacaGfgAfgUfcaggaa*a*a	1261	AV05303-AS	u*Uf*uuccUfgacuCfcUfgUfuuc*u*c	1562
AV05304	AV05304-SS	c*c*cuaagaAfgUfuCfccuggu*u*a	1262	AV05304-AS	u*Af*acCfa(gUNA)ggaaCfuUfcUfuag*g*g	1563
AV05305	AV05305-SS	g*a*guucccUfgGfuUfuuuccc*a*a	1263	AV05305-AS	u*Uf*gggaAfaaacCfaGfgGfaac*u*c	1564
AV05306	AV05306-SS	g*g*uucccuGfgUfuUfuuccca*g*a	1264	AV05306-AS	u*Cf*ugGfg(aUNA)aaaaCfcAfgGfgaa*c*c	1565
AV05307	AV05307-SS	c*g*gagacaAfgCfaUfuuauac*u*a	1265	AV05307-AS	u*Af*guauAfaaugCfuUfgUfcuc*c*g	1566
AV05308	AV05308-SS	g*g*aaacgaGfgUfuUfcaacau*g*a	1266	AV05308-AS	u*Cf*auguUfgaaaCfcUfcGfuuu*c*c	1567
AV05309	AV05309-SS	g*g*ccuggcUfuAfuAfcuuucu*u*a	1267	AV05309-AS	u*Af*agaaAfguauAfaGfcCfagg*c*c	1568
AV05310	AV05310-SS	c*c*cuggcuUfaUfaCfuuucuu*a*a	1268	AV05310-AS	u*Uf*aagaAfaguaUfaAfgCfcag*g*g	1569
AV05311	AV05311-SS	g*u*ggcuuaUfaCfuUfucuuaa*u*a	1269	AV05311-AS	u*Af*uuaaGfaaagUfaUfaAfgcc*a*c	1570
AV05312	AV05312-SS	c*g*cuuauaCfuUfuCfuuaaua*a*a	1270	AV05312-AS	u*Uf*uauuAfagaaAfgUfaUfaag*c*g	1571
AV05313	AV05313-SS	g*u*uauacuUfuCfuUfaauaaa*a*a	1271	AV05313-AS	u*Uf*uuuaUfuaagAfaAfgUfaua*a*c	1572
AV05314	AV05314-SS	g*a*cuuucuUfaAfuAfaaaagg*a*a	1272	AV05314-AS	u*Uf*ccuuUfuuauUfaAfgAfaag*u*c	1573
AV05315	AV05315-SS	g*u*cuuaauAfaAfaAfggagaa*a*a	1273	AV05315-AS	u*Uf*uucuCfcuuuUfuAfuUfaag*a*c	1574
AV05316	AV05316-SS	g*c*uuaauaAfaAfaGfgagaaa*g*a	1274	AV05316-AS	u*Cf*uuucUfccuuUfuUfaUfuaa*g*c	1575
AV06796	AV06796-SS	c*u*gcuggaGfcUfaGfccaagc*a*a	1275	AV06796-AS	u*Uf*gcUfu(gUNA)gcuaGfcUfcCfagc*a*g	1576
AV06797	AV06797-SS	c*c*caagcaGfcAfaAfuccugg*a*a	1276	AV06797-AS	u*Uf*ccAfg(gUNA)auuuGfcUfgCfuug*g*g	1577
AV06798	AV06798-SS	g*a*gucgucCfcAfgAfauaacu*c*a	1277	AV06798-AS	u*Gf*agUfu(aUNA)uucuGfgGfaCfgac*u*c	1578
AV06799	AV06799-SS	c*a*ccagagCfcCfuCfcggaga*c*a	1278	AV06799-AS	u*Gf*ucUfc(cUNA)ggagGfgCfuCfugg*u*g	1579
AV06800	AV06800-SS	c*a*ggucauCfaGfcUfuugcua*c*a	1279	AV06800-AS	u*Gf*uaGfc(aUNA)aagcUfgAfuGfacc*u*g	1580
AV06801	AV06801-SS	g*a*ccugucCfaCfuCfcucggu*c*a	1280	AV06801-AS	u*Gf*acCfg(aUNA)ggagUfgGfaCfagg*u*c	1581
AV06802	AV06802-SS	g*u*guccacUfcCfuCfgguccc*a*a	1281	AV06802-AS	u*Uf*ggGfa(cUNA)cgagGfaGfuGfgac*a*c	1582
AV06803	AV06803-SS	g*c*caccacCfuGfuAfccaugc*c*a	1282	AV06803-AS	u*Gf*gcAfu(gUNA)guacAfgGfuGfgug*g*c	1583
AV06804	AV06804-SS	c*c*uccccaCfcCfuUfccuggc*a*a	1283	AV06804-AS	u*Uf*gcCfa(gUNA)gaagGfgUfgGfgga*g*g	1584
AV06805	AV06805-SS	g*u*ccccacCfcUfuCfcuggca*c*a	1284	AV06805-AS	u*Gf*ugCfc(aUNA)ggaaGfgGfuGfggg*a*c	1585
AV06806	AV06806-SS	g*c*ucuuugCfuUfgAfggaucu*u*a	1285	AV06806-AS	u*Af*agAfu(cUNA)cucaAfgCfaAfaga*g*c	1586
AV06807	AV06807-SS	g*u*ugaggaUfcUfuCfcgaugg*g*a	1286	AV06807-AS	u*Cf*ccAfu(cUNA)ggaaGfaUfcCfuca*a*c	1587
AV06808	AV06808-SS	c*g*aucuucCfgAfuGfggacc*a*a	1287	AV06808-AS	u*Uf*ggUfc(cUNA)ccauCfgGfaAfgau*c*g	1588

AV06809	AV06809-SS	g*u*ggcugaGfcAfcCfacauca*c*a	1288	AV06809-AS	u*Gf*ugAfu(gUNA)uggu GfcUfcAfgcc*a*c	1589
AV06810	AV06810-SS	c*a*gcaccaCfaUfcAfccaacc*u*a	1289	AV06810-AS	u*Af*ggUfu(gUNA)gugaU fgUfgGfugc*u*g	1590
AV06811	AV06811-SS	c*c*accacaUfcAfcCfaaccug*g*a	1290	AV06811-AS	u*Cf*caGfg(uUNA)ugguG faUfgUfggu*g*g	1591
AV06812	AV06812-SS	g*a*uaccuuAfaCfuCfugcccu*c*a	1291	AV06812-AS	u*Gf*agGfg(cUNA)agagU fuAfaGfgua*u*c	1592
AV06813	AV06813-SS	g*u*accuuaAfcUfcUfgcccuc*u*a	1292	AV06813-AS	u*Af*gaGfg(gUNA)cagaG fuUfaAfggu*a*c	1593
AV06814	AV06814-SS	c*c*ccucuaGfuGfgCfuugagg*g*a	1293	AV06814-AS	u*Cf*ccUfc(aUNA)agccAf cUfaGfagg*g*g	1594
AV06815	AV06815-SS	g*c*ucuaguGfgCfuUfgagggg*u*a	1294	AV06815-AS	u*Af*ccCfc(uUNA)caagCf cAfcUfaga*g*c	1595
AV06816	AV06816-SS	c*g*gugagaAfgUfcUfgguguc*c*a	1295	AV06816-AS	u*Gf*gaCfa(cUNA)cagaCf uUfcUfcac*c*g	1596
AV06817	AV06817-SS	c*u*cuggugUfcCfuGfaaacug*c*a	1296	AV06817-AS	u*Gf*caGfu(uUNA)ucagG faCfaCfcag*a*g	1597
AV06818	AV06818-SS	g*c*ugguguCfcUfgAfaacugc*a*a	1297	AV06818-AS	u*Uf*gcAfg(uUNA)uucaG fgAfcAfcca*g*c	1598
AV06819	AV06819-SS	g*u*ggugucCfuGfaAfacugca*a*a	1298	AV06819-AS	u*Uf*ugCfa(gUNA)uuucA fgGfaCfacc*a*c	1599
AV06820	AV06820-SS	g*c*ugcagaCfcCfcUfagaagg*c*a	1299	AV06820-AS	u*Gf*ccUfu(cUNA)uaggG fgUfcUfgca*g*c	1600
AV06821	AV06821-SS	g*u*gcagacCfcCfuAfgaaggc*a*a	1300	AV06821-AS	u*Uf*gcCfu(uUNA)cuagG fgGfuCfugc*a*c	1601
AV06822	AV06822-SS	g*c*agcacaGfuUfaCfuggaca*a*a	1301	AV06822-AS	u*Uf*ugUfc(cUNA)aguaA fcUfgUfgcu*g*c	1602
AV06823	AV06823-SS	g*a*gcacagUfuAfcUfggacaa*c*a	1302	AV06823-AS	u*Gf*uuGfu(cUNA)caguA faCfuGfugc*u*c	1603
AV06824	AV06824-SS	g*g*gacacaGfcAfgGfacacca*g*a	1303	AV06824-AS	u*Cf*ugGfu(gUNA)uccuG fcUfgUfguc*c*c	1604
AV06825	AV06825-SS	c*g*acaccaGfcAfgCfccuucc*u*a	1304	AV06825-AS	u*Af*ggAfa(gUNA)ggcuG fcUfgGfugu*c*g	1605
AV06826	AV06826-SS	g*c*cagcagCfcCfuUfccuaga*g*a	1305	AV06826-AS	u*Cf*ucUfa(gUNA)gaagG fgCfuGfcug*g*c	1606
AV06827	AV06827-SS	g*c*agcagcCfcUfuCfcuagag*c*a	1306	AV06827-AS	u*Gf*cuCfu(aUNA)ggaaG fgGfcUfgcu*g*c	1607
AV06828	AV06828-SS	c*c*agcccuUfcCfuAfgagcuu*a*a	1307	AV06828-AS	u*Uf*aaGfc(uUNA)cuagG faAfgGfgcu*g*g	1608
AV06829	AV06829-SS	g*g*agcuuaAfgAfuCfcgagcc*a*a	1308	AV06829-AS	u*Uf*ggCfu(cUNA)ggauC fuUfaAfgcu*c*c	1609
AV06830	AV06830-SS	g*u*ccgagcCfaAfuGfagccug*g*a	1309	AV06830-AS	u*Cf*caGfg(cUNA)ucauU fgGfcUfcgg*a*c	1610
AV06831	AV06831-SS	g*c*gagccaAfuGfaGfccugga*g*a	1310	AV06831-AS	u*Cf*ucCfa(gUNA)gcucA fuUfgGfcuc*g*c	1611
AV06832	AV06832-SS	g*g*agccaaUfgAfgCfcuggag*c*a	1311	AV06832-AS	u*Gf*cuCfc(aUNA)ggcuC faUfuGfgcu*c*c	1612
AV06833	AV06833-SS	g*c*cccuuaUfgUfuGfcaggcg*a*a	1312	AV06833-AS	u*Uf*cgCfc(uUNA)gcaaCf aUfaAfggg*g*c	1613
AV06834	AV06834-SS	c*a*ccauuaCfgUfaGfacuucc*a*a	1313	AV06834-AS	u*Uf*ggAfa(gUNA)ucuaC fgUfaAfugg*u*g	1614
AV06835	AV06835-SS	g*u*uccaggAfaCfuGfggaugg*c*a	1314	AV06835-AS	u*Gf*ccAfu(cUNA)ccagU fuCfcUfgga*a*c	1615
AV06836	AV06836-SS	c*a*gggguaCfcAfgCfugaauu*a*a	1315	AV06836-AS	u*Uf*aaUfu(cUNA)agcuG fgUfaCfccc*u*g	1616
AV06837	AV06837-SS	g*c*agcugaAfuUfaCfugcagu*g*a	1316	AV06837-AS	u*Cf*acUfg(cUNA)aguaA fuUfcAfgcu*g*c	1617

AV06838	AV06838-SS	g*g*cugaauUfaCfuGfcagugg*g*a	1317	AV06838-AS	u*Cf*ccAfc(uUNA)gcagUfaAfuUfcag*c*c	1618
AV06839	AV06839-SS	g*a*gcccagGfcAfuUfgcugcc*u*a	1318	AV06839-AS	u*Af*ggCfa(gUNA)caauGfcCfuGfggc*u*c	1619
AV06840	AV06840-SS	g*c*aggcauUfgCfuGfccucuu*u*a	1319	AV06840-AS	u*Af*aaGfa(gUNA)gcagCfaAfuGfccu*g*c	1620
AV06841	AV06841-SS	c*c*auugcuGfcCfuCfuuucca*u*a	1320	AV06841-AS	u*Af*ugGfa(aUNA)agagGfcAfgCfaau*g*g	1621
AV06842	AV06842-SS	g*u*gccucuUfuCfcAfuucugc*c*a	1321	AV06842-AS	u*Gf*gcAfg(aUNA)auggAfaAfgAfggc*a*c	1622
AV06843	AV06843-SS	c*c*cucuuuCfcAfuUfcugccg*u*a	1322	AV06843-AS	u*Af*cgGfc(aUNA)gaauGfgAfaAfgag*g*g	1623
AV06844	AV06844-SS	g*c*ucuuucCfaUfuCfugccgu*c*a	1323	AV06844-AS	u*Gf*acGfg(cUNA)agaaUfgGfaAfaga*g*c	1624
AV06845	AV06845-SS	g*u*cugccgUfcUfuCfagccuc*c*a	1324	AV06845-AS	u*Gf*gaGfg(cUNA)ugaaGfaCfgGfcag*a*c	1625
AV06846	AV06846-SS	g*u*ucagccUfcCfuCfaaagcc*a*a	1325	AV06846-AS	u*Uf*ggCfu(uUNA)ugagGfaGfgCfuga*a*c	1626
AV06847	AV06847-SS	g*a*agccaaCfaAfuCfcuuggc*c*a	1326	AV06847-AS	u*Gf*gcCfa(aUNA)ggauUfgUfuGfgcu*u*c	1627
AV06848	AV06848-SS	g*g*ccaacaAfuCfcUfuggccu*g*a	1327	AV06848-AS	u*Cf*agGfc(cUNA)aaggAfuUfgUfugg*c*c	1628
AV06849	AV06849-SS	g*g*ugucccUfaCfuGfcccgaa*g*a	1328	AV06849-AS	u*Cf*uuCfg(gUNA)gcagUfaGfgGfaca*c*c	1629
AV06850	AV06850-SS	g*c*ucucucUfcCfuCfuaccug*g*a	1329	AV06850-AS	u*Cf*caGfg(uUNA)agagGfaGfaGfaga*g*c	1630
AV06851	AV06851-SS	g*u*cucucuCfcUfcUfaccugg*a*a	1330	AV06851-AS	u*Uf*ccAfg(gUNA)uagaGfgAfgAfgag*a*c	1631
AV06852	AV06852-SS	g*c*ucucucCfuCfuAfccugga*u*a	1331	AV06852-AS	u*Af*ucCfa(gUNA)guagAfgGfaGfaga*g*c	1632
AV06853	AV06853-SS	g*c*ucuccuCfuAfcCfuggauc*a*a	1332	AV06853-AS	u*Uf*gaUfc(cUNA)agguAfgAfgGfaga*g*c	1633
AV06854	AV06854-SS	g*u*cuaccuGfgAfuCfauaaug*g*a	1333	AV06854-AS	u*Cf*caUfu(aUNA)ugauCfcAfgGfuag*a*c	1634
AV06855	AV06855-SS	g*a*ccuggaUfcAfuAfauggca*a*a	1334	AV06855-AS	u*Uf*ugCfc(aUNA)uuauGfaUfcCfagg*u*c	1635
AV06856	AV06856-SS	g*a*ugugguCfaAfgAfcggaug*u*a	1335	AV06856-AS	u*Af*caUfc(cUNA)gucuUfgAfcCfaca*u*c	1636
AV06857	AV06857-SS	g*g*uggucaAfgAfcGfgaugug*c*a	1336	AV06857-AS	u*Gf*caCfa(uUNA)ccguCfuUfgAfcca*c*c	1637
AV06858	AV06858-SS	c*u*caagacGfgAfuGfugccag*a*a	1337	AV06858-AS	u*Uf*cuGfg(cUNA)acauCfcGfuCfuug*a*g	1638
AV06859	AV06859-SS	g*a*gacggaUfgUfgCfcagaua*u*a	1338	AV06859-AS	u*Af*uaUfc(uUNA)ggcaCfaUfcCfguc*u*c	1639
AV06860	AV06860-SS	g*c*ggauguGfcCfaGfauaugg*u*a	1339	AV06860-AS	u*Af*ccAfu(aUNA)ucugGfcAfcAfucc*g*c	1640
AV06861	AV06861-SS	c*u*gccagaUfaUfgGfuggugg*a*a	1340	AV06861-AS	u*Uf*ccAfc(cUNA)accaUfaUfcUfggc*a*g	1641
AV06862	AV06862-SS	c*g*gcuuugGfaGfuGfaagaga*c*a	1341	AV06862-AS	u*Gf*ucUfc(uUNA)ucacUfcCfaAfagc*c*g	1642
AV06863	AV06863-SS	c*c*uuuggaGfuGfaAfgagacc*a*a	1342	AV06863-AS	u*Uf*ggUfc(uUNA)cuucAfcUfcCfaaa*g*g	1643
AV06864	AV06864-SS	g*u*uggaguGfaAfgAfgaccaa*g*a	1343	AV06864-AS	u*Cf*uuGfg(uUNA)cucuUfcAfcUfcca*a*c	1644
AV06865	AV06865-SS	g*g*gagugaAfgAfgAfccaaga*u*a	1344	AV06865-AS	u*Af*ucUfu(gUNA)gucuCfuUfcAfcuc*c*c	1645
AV06866	AV06866-SS	c*a*gaccaaGfaUfgAfaguuuc*c*a	1345	AV06866-AS	u*Gf*gaAfa(cUNA)uucaUfcUfuGfguc*u*g	1646

AV06867	AV06867-SS	g*g*accaagAfuGfaAfguuucc*c*a	1346	AV06867-AS	u*Gf*ggAfa(aUNA)cuucAfuCfuUfggu*c*c	1647
AV06868	AV06868-SS	g*c*aagaugAfaGfuUfucccag*g*a	1347	AV06868-AS	u*Cf*cuGfg(gUNA)aaacUfuCfaUfcuu*g*c	1648
AV06869	AV06869-SS	c*a*ugaaguUfuCfcCfaggcac*a*a	1348	AV06869-AS	u*Uf*guGfc(cUNA)ugggAfaAfcUfuca*u*g	1649
AV06870	AV06870-SS	c*u*uucccaGfgCfaCfaggca*u*a	1349	AV06870-AS	u*Af*ugCfc(cUNA)ugugCfcUfgGfgaa*a*g	1650
AV06871	AV06871-SS	g*u*ucccagGfcAfcAfggcau*c*a	1350	AV06871-AS	u*Gf*auGfc(cUNA)cuguGfcCfuGfgga*a*c	1651
AV06872	AV06872-SS	g*c*ccaggcAfcAfgGfgcaucu*g*a	1351	AV06872-AS	u*Cf*agAfu(gUNA)cccuGfuGfcCfugg*g*c	1652
AV06873	AV06873-SS	g*g*acuggaGfgCfaUfcagauu*c*a	1352	AV06873-AS	u*Gf*aaUfc(uUNA)gaugCfcUfcCfagu*c*c	1653
AV06874	AV06874-SS	g*c*uggaggCfaUfcAfgauucc*u*a	1353	AV06874-AS	u*Af*ggAfa(uUNA)cugaUfgCfcUfcca*g*c	1654
AV06875	AV06875-SS	g*g*gaggcaUfcAfgAfuuccug*a*a	1354	AV06875-AS	u*Uf*caGfg(aUNA)aucuGfaUfgCfcuc*c*c	1655
AV06876	AV06876-SS	c*a*uccacaCfcCfcAfaccaa*c*a	1355	AV06876-AS	u*Gf*uuGfg(gUNA)uuggGfgUfgUfgga*u*g	1656
AV06877	AV06877-SS	g*c*accccaAfcCfcAfacaacc*a*a	1356	AV06877-AS	u*Uf*ggUfu(gUNA)uuggGfuUfgGfggu*g*c	1657
AV06878	AV06878-SS	g*a*ccccaaCfcCfaAfcaacca*c*a	1357	AV06878-AS	u*Gf*ugGfu(uUNA)guugGfgUfuGfggg*u*c	1658
AV06879	AV06879-SS	g*c*aacccaAfcAfaCfccaccug*g*a	1358	AV06879-AS	u*Cf*caGfg(uUNA)gguuGfuUfgGfguu*g*c	1659
AV06880	AV06880-SS	g*a*cccaacAfaCfcAfccuggc*a*a	1359	AV06880-AS	u*Uf*gcCfa(gUNA)guggUfuGfuUfggg*u*c	1660
AV06881	AV06881-SS	g*c*ccaacaAfcCfaCfcuggca*a*a	1360	AV06881-AS	u*Uf*ugCfc(aUNA)ggugGfuUfgUfugg*g*c	1661
AV06882	AV06882-SS	g*c*caacaaCfcAfcCfuggcaa*u*a	1361	AV06882-AS	u*Af*uuGfc(cUNA)agguGfgUfuGfuug*g*c	1662
AV06883	AV06883-SS	g*a*accaccUfgGfcAfauauga*c*a	1362	AV06883-AS	u*Gf*ucAfu(aUNA)uugcCfaGfgUfggu*u*c	1663
AV06884	AV06884-SS	g*a*ccaccuGfgCfaAfuaugac*u*a	1363	AV06884-AS	u*Af*guCfa(uUNA)auugCfcAfgGfugg*u*c	1664
AV06885	AV06885-SS	g*c*caccugGfcAfaUfaugacu*c*a	1364	AV06885-AS	u*Gf*agUfc(aUNA)uauuGfcCfaGfgug*g*c	1665
AV06886	AV06886-SS	g*c*accuggCfaAfuAfugacuc*a*a	1365	AV06886-AS	u*Uf*gaGfu(cUNA)auauUfgCfcAfggu*g*c	1666
AV06887	AV06887-SS	g*a*ccuggcAfaUfaUfgacuca*c*a	1366	AV06887-AS	u*Gf*ugAfg(uUNA)cauaUfuGfcCfagg*u*c	1667
AV06888	AV06888-SS	c*c*aauaugAfcUfcAfcuugac*c*a	1367	AV06888-AS	u*Gf*guCfa(aUNA)gugaGfuCfaUfauu*g*g	1668
AV06889	AV06889-SS	g*u*augacuCfaCfuUfgacccc*u*a	1368	AV06889-AS	u*Af*ggGfg(uUNA)caagUfgAfgUfcau*a*c	1669
AV06890	AV06890-SS	c*a*cccaaaUfgGfgCfacuuuc*u*a	1369	AV06890-AS	u*Af*gaAfa(gUNA)ugccCfaUfuUfggg*u*g	1670
AV06891	AV06891-SS	g*c*ccaaauGfgGfcAfcuuucu*u*a	1370	AV06891-AS	u*Af*agAfa(aUNA)gugcCfcAfuUfugg*g*c	1671
AV06892	AV06892-SS	g*c*caaaugGfgCfaCfuuucuu*g*a	1371	AV06892-AS	u*Cf*aaGfa(aUNA)agugCfcCfaUfuug*g*c	1672
AV06893	AV06893-SS	g*g*ggcacuUfuCfuUfgucuga*g*a	1372	AV06893-AS	u*Cf*ucAfg(aUNA)caagAfaAfgUfgcc*c*c	1673
AV06894	AV06894-SS	g*a*uuccagGfuUfgGfcugaug*u*a	1373	AV06894-AS	u*Af*caUfc(aUNA)gccaAfcCfuGfgaa*u*c	1674
AV06895	AV06895-SS	g*u*uagccuCfuCfcCfaagaug*a*a	1374	AV06895-AS	u*Uf*caUfc(uUNA)ugggAfgAfgGfcua*a*c	1675

AV06896	AV06896-SS	g*a*gccucuCfcCfaAfgaugag*a*a	1375	AV06896-AS	u*Uf*cuCfa(uUNA)cuugGfgAfgAfggc*u*c	1676
AV06897	AV06897-SS	g*u*cccaagAfuGfaGfaaaguc*c*a	1376	AV06897-AS	u*Gf*gaCfu(uUNA)ucucAfuCfuUfggg*a*c	1677
AV06898	AV06898-SS	g*c*ccaagaUfgAfgAfaagucc*u*a	1377	AV06898-AS	u*Af*ggAfc(uUNA)uucuCfaUfcUfugg*g*c	1678
AV06899	AV06899-SS	g*g*gaggaaGfcAfgAfuagaug*g*a	1378	AV06899-AS	u*Cf*caUfc(uUNA)aucuGfcUfuCfcuc*c*c	1679
AV06900	AV06900-SS	c*g*aagcagAfuAfgAfuggucc*a*a	1379	AV06900-AS	u*Uf*ggAfc(cUNA)aucuAfuCfuGfcuu*c*g	1680
AV06901	AV06901-SS	g*a*gcagauAfgAfuGfguccag*c*a	1380	AV06901-AS	u*Gf*cuGfg(aUNA)ccauCfuAfuCfugc*u*c	1681
AV06902	AV06902-SS	g*g*cagauaGfaUfgGfuccagc*a*a	1381	AV06902-AS	u*Uf*gcUfg(gUNA)accaUfcUfaUfcug*c*c	1682
AV06903	AV06903-SS	c*a*ugguccAfgCfaGfgcuuga*a*a	1382	AV06903-AS	u*Uf*ucAfa(gUNA)ccugCfuGfgAfcca*u*g	1683
AV06904	AV06904-SS	c*g*cuugaaGfcAfgGfguaagc*a*a	1383	AV06904-AS	u*Uf*gcUfu(aUNA)cccuGfcUfuCfaag*c*g	1684
AV06905	AV06905-SS	c*g*gaagguCfaAfgAfggaga*u*a	1384	AV06905-AS	u*Af*ucUfc(cUNA)cucuUfgAfcCfuuc*c*g	1685
AV06906	AV06906-SS	c*a*aggucaAfgAfgGfgagaug*g*a	1385	AV06906-AS	u*Cf*caUfc(uUNA)cccuCfuUfgAfccu*u*g	1686
AV06907	AV06907-SS	g*c*ccagaaAfcAfgGfagucag*g*a	1386	AV06907-AS	u*Cf*cuGfa(cUNA)uccuGfuUfuCfugg*g*c	1687
AV06908	AV06908-SS	g*c*cagaaaCfaGfgAfgucagg*a*a	1387	AV06908-AS	u*Uf*ccUfg(aUNA)cuccUfgUfuUfcug*g*c	1688
AV06909	AV06909-SS	g*c*agaaacAfgGfaGfucagga*a*a	1388	AV06909-AS	u*Uf*ucCfu(gUNA)acucCfuGfuUfucu*g*c	1689
AV06910	AV06910-SS	g*g*gcacuaAfgCfcUfaagaag*u*a	1389	AV06910-AS	u*Af*cuUfc(uUNA)uaggCfuUfaGfugc*c*c	1690
AV06911	AV06911-SS	g*a*agccuaAfgAfaGfuucccu*g*a	1390	AV06911-AS	u*Cf*agGfg(aUNA)acuuCfuUfaGfgcu*u*c	1691
AV06912	AV06912-SS	g*g*ccuaagAfaGfuUfccccugg*u*a	1391	AV06912-AS	u*Af*ccAfg(gUNA)gaacUfuCfuUfagg*c*c	1692
AV06913	AV06913-SS	g*c*uaagaaGfuUfcCfcugguu*u*a	1392	AV06913-AS	u*Af*aaCfc(aUNA)gggaAfcUfuCfuua*g*c	1693
AV06914	AV06914-SS	g*u*aagaagUfuCfcCfugguuu*u*a	1393	AV06914-AS	u*Af*aaAfc(cUNA)agggAfaCfuUfcuu*a*c	1694
AV06915	AV06915-SS	g*a*agaaguUfcCfcUfgguuuu*u*a	1394	AV06915-AS	u*Af*aaAfa(cUNA)caggGfaAfcUfucu*u*c	1695
AV06916	AV06916-SS	g*a*gaaguuCfcCfuGfguuuuu*c*a	1395	AV06916-AS	u*Gf*aaaaAfccagGfgAfaCfuuc*u*c	1696
AV06917	AV06917-SS	g*g*aaguucCfcUfgGfuuuuuc*c*a	1396	AV06917-AS	u*Gf*gaAfa(aUNA)accaGfgGfaAfcuu*c*c	1697
AV06918	AV06918-SS	c*u*ucccugGfuUfuUfucccag*g*a	1397	AV06918-AS	u*Cf*cuGfg(gUNA)aaaaAfcCfaGfgga*a*g	1698
AV06919	AV06919-SS	c*g*acaggaCfcCfaCfugggag*a*a	1398	AV06919-AS	u*Uf*cuCfc(cUNA)agugGfgUfcCfugu*c*g	1699
AV06920	AV06920-SS	c*a*gacaagCfaUfuUfauacuu*u*a	1399	AV06920-AS	u*Af*aaGfu(aUNA)uaaaUfgCfuUfguc*u*g	1700
AV06921	AV06921-SS	g*c*ucuugaUfcCfaCfccgacu*u*a	1400	AV06921-AS	u*Af*agUfc(gUNA)ggugGfaUfcAfaga*g*c	1701
AV06922	AV06922-SS	g*c*gcgccuGfgCfuUfauacuu*u*a	1401	AV06922-AS	u*Af*aaGfu(aUNA)uaagCfcAfgGfcgc*g*c	1702
AV06923	AV06923-SS	g*g*cgccugGfcUfuAfuacuuu*c*a	1402	AV06923-AS	u*Gf*aaAfg(uUNA)auaaGfcCfaGfgcg*c*c	1703
AV06924	AV06924-SS	c*c*gccuggCfuUfaUfacuuuc*u*a	1403	AV06924-AS	u*Af*gaAfa(gUNA)uauaAfgCfcAfggc*g*g	1704

AV06925	AV06925-SS	g*c*uggcuuAfuAfcUfuucuua*a*a	1404	AV06925-AS	u*Uf*uaAfg(aUNA)aaguAfuAfaGfcca*g*c	1705
AV06926	AV06926-SS	g*c*uuucuuAfaUfaAfaaagga*g*a	1405	AV06926-AS	u*Cf*uccuUfuuuaUfuAfaGfaaa*g*c	1706
AV06927	AV06927-SS	g*u*agccaaGfcAfgCfaaaucc*u*a	1406	AV06927-AS	u*Af*ggAfu(uUNA)ugcuGfcUfuGfgcu*a*c	1707
AV06928	AV06928-SS	g*c*agucguCfcCfaGfaauaac*u*a	1407	AV06928-AS	u*Af*guUfa(uUNA)ucugGfgAfcGfacu*g*c	1708
AV06929	AV06929-SS	c*u*cccaccAfcCfuGfuaccau*g*a	1408	AV06929-AS	u*Cf*auGfg(uUNA)acagGfuGfgUfggg*a*g	1709
AV06930	AV06930-SS	g*u*uccuggCfaCfuCfuuugcu*u*a	1409	AV06930-AS	u*Af*agCfa(aUNA)agagUfgCfcAfgga*a*c	1710
AV06931	AV06931-SS	g*c*cuggcaCfuCfuUfugcuug*a*a	1410	AV06931-AS	u*Uf*caAfg(cUNA)aaagAfgUfgCfcag*g*c	1711
AV06932	AV06932-SS	c*g*cacucuUfuGfcUfugagga*u*a	1411	AV06932-AS	u*Af*ucCfu(cUNA)aagcAfaAfgAfgug*c*g	1712
AV06933	AV06933-SS	g*a*cucuuuGfcUfuGfaggauc*u*a	1412	AV06933-AS	u*Af*gaUfc(cUNA)ucaaGfcAfaAfgag*u*c	1713
AV06934	AV06934-SS	g*u*gcuugaGfgAfuCfuuccga*u*a	1413	AV06934-AS	u*Af*ucGfg(aUNA)agauCfcUfcAfagc*a*c	1714
AV06935	AV06935-SS	c*a*gaagucUfgGfuGfuccuga*a*a	1414	AV06935-AS	u*Uf*ucAfg(gUNA)acacCfaGfaCfuuc*u*g	1715
AV06936	AV06936-SS	c*a*agucugGfuGfuCfcugaaa*c*a	1415	AV06936-AS	u*Gf*uuUfc(aUNA)ggacAfcCfaGfacu*u*g	1716
AV06937	AV06937-SS	g*a*gucuggUfgUfcCfugaaac*u*a	1416	AV06937-AS	u*Af*guUfu(cUNA)aggaCfaCfcAfgac*u*c	1717
AV06938	AV06938-SS	c*g*uguccuGfaAfaCfugcaac*u*a	1417	AV06938-AS	u*Af*guUfg(cUNA)aguuUfcAfgGfaca*c*g	1718
AV06939	AV06939-SS	c*u*guccugAfaAfcUfgcaacu*a*a	1418	AV06939-AS	u*Uf*agUfu(gUNA)caguUfuCfaGfgac*a*g	1719
AV06940	AV06940-SS	g*g*uccugaAfaCfuGfcaacua*g*a	1419	AV06940-AS	u*Cf*uaGfu(uUNA)gcagUfuUfcAfgga*c*c	1720
AV06941	AV06941-SS	c*u*ccugaaAfcUfgCfaacuag*a*a	1420	AV06941-AS	u*Uf*cuAfg(uUNA)ugcaGfuUfuCfagg*a*g	1721
AV06942	AV06942-SS	g*c*cugaaaCfuGfcAfacuaga*c*a	1421	AV06942-AS	u*Gf*ucUfa(gUNA)uugcAfgUfuUfcag*g*c	1722
AV06943	AV06943-SS	g*c*ugaaacUfgCfaAfcuagac*u*a	1422	AV06943-AS	u*Af*guCfu(aUNA)guugCfaGfuUfuca*g*c	1723
AV06944	AV06944-SS	g*c*uuccuaGfaGfcUfuaagau*c*a	1423	AV06944-AS	u*Gf*auCfu(uUNA)aagcUfcUfaGfgaa*g*c	1724
AV06945	AV06945-SS	g*u*uccuagAfgCfuUfaagauc*c*a	1424	AV06945-AS	u*Gf*gaUfc(uUNA)uaagCfuCfuAfgga*a*c	1725
AV06946	AV06946-SS	g*g*cuuaagAfuCfcGfagccaa*u*a	1425	AV06946-AS	u*Af*uuGfg(cUNA)ucggAfuCfuUfaag*c*c	1726
AV06947	AV06947-SS	g*u*gcgaccCfcCfuUfauguug*c*a	1426	AV06947-AS	u*Gf*caAfc(aUNA)uaagGfgGfgUfcgc*a*c	1727
AV06948	AV06948-SS	g*g*cgacccCfcUfuAfuguugc*a*a	1427	AV06948-AS	u*Uf*gcAfa(cUNA)auaaGfgGfgGfucg*c*c	1728
AV06949	AV06949-SS	c*a*gaccauUfaCfgUfagacuu*c*a	1428	AV06949-AS	u*Gf*aaGfu(cUNA)uacgUfaAfuGfguc*u*g	1729
AV06950	AV06950-SS	g*a*cguagaCfuUfcCfaggaac*u*a	1429	AV06950-AS	u*Af*guUfc(cUNA)uggaAfgUfcUfacg*u*c	1730
AV06951	AV06951-SS	c*g*gguaccAfgCfuGfaauuac*u*a	1430	AV06951-AS	u*Af*guAfa(uUNA)ucagCfuGfgUfacc*c*g	1731
AV06952	AV06952-SS	c*u*accagcUfgAfaUfuacugc*a*a	1431	AV06952-AS	u*Uf*gcAfg(uUNA)aauuCfaGfcUfggu*a*g	1732
AV06953	AV06953-SS	g*a*uugcugCfcUfcUfuuccau*u*a	1432	AV06953-AS	u*Af*auGfg(aUNA)aagaGfgCfaGfcaa*u*c	1733

AV06954	AV06954-SS	g*u*ugcugcCfuCfuUfuccauu*c*a	1433	AV06954-AS	u*Gf*aaUfg(gUNA)aaagAfgGfcAfgca*a*c	1734
AV06955	AV06955-SS	g*u*gcugccUfcUfuUfccauuc*u*a	1434	AV06955-AS	u*Af*gaAfu(gUNA)gaaaGfaGfgCfagc*a*c	1735
AV06956	AV06956-SS	g*g*cugccuCfuUfuCfcauucu*g*a	1435	AV06956-AS	u*Cf*agAfa(uUNA)ggaaAfgAfgGfcag*c*c	1736
AV06957	AV06957-SS	g*g*ucuucaGfcCfuCfcucaaa*g*a	1436	AV06957-AS	u*Cf*uuUfg(aUNA)ggagGfcUfgAfaga*c*c	1737
AV06958	AV06958-SS	g*u*ccucaaAfgCfcAfacaauc*c*a	1437	AV06958-AS	u*Gf*gaUfu(gUNA)uuggCfuUfuGfagg*a*c	1738
AV06959	AV06959-SS	g*c*cucaaaGfcCfaAfcaaucc*u*a	1438	AV06959-AS	u*Af*ggAfu(uUNA)guugGfcUfuUfgag*g*c	1739
AV06960	AV06960-SS	g*u*cuccucUfaCfcUfggauca*u*a	1439	AV06960-AS	u*Af*ugAfu(cUNA)caggUfaGfaGfgag*a*c	1740
AV06961	AV06961-SS	g*c*uccucuAfcCfuGfgaucau*a*a	1440	AV06961-AS	u*Uf*auGfa(uUNA)ccagGfuAfgAfgga*g*c	1741
AV06962	AV06962-SS	g*u*ccucuaCfcUfgGfaucaua*a*a	1441	AV06962-AS	u*Uf*uaUfg(aUNA)uccaGfgUfaGfagg*a*c	1742
AV06963	AV06963-SS	g*c*ucuaccUfgGfaUfcauaau*g*a	1442	AV06963-AS	u*Cf*auUfa(uUNA)gaucCfaGfgUfaga*g*c	1743
AV06964	AV06964-SS	g*u*ggaucaUfaAfuGfgcaaug*u*a	1443	AV06964-AS	u*Af*caUfu(gUNA)ccauUfaUfgAfucc*a*c	1744
AV06965	AV06965-SS	g*g*gaucauAfaUfgGfcaaugu*g*a	1444	AV06965-AS	u*Cf*acAfu(uUNA)gccaUfuAfuGfauc*c*c	1745
AV06966	AV06966-SS	c*g*aucauaAfuGfgCfaaugug*g*a	1445	AV06966-AS	u*Cf*caCfa(uUNA)ugccAfuUfaUfgau*c*g	1746
AV06967	AV06967-SS	g*a*uaauggCfaAfuGfugguca*a*a	1446	AV06967-AS	u*Uf*ugAfc(cUNA)acauUfgCfcAfuua*u*c	1747
AV06968	AV06968-SS	g*a*auggcaAfuGfuGfgucaag*a*a	1447	AV06968-AS	u*Uf*cuUfg(aUNA)ccacAfuUfgCfcau*u*c	1748
AV06969	AV06969-SS	g*a*agacggAfuGfuGfccagau*a*a	1448	AV06969-AS	u*Uf*auCfu(gUNA)gcacAfuCfcGfucu*u*c	1749
AV06970	AV06970-SS	g*u*ggagugAfaGfaGfaccaag*a*a	1449	AV06970-AS	u*Uf*cuUfg(gUNA)ucucUfuCfaCfucc*a*c	1750
AV06971	AV06971-SS	c*g*agugaaGfaGfaCfcaagau*g*a	1450	AV06971-AS	u*Cf*auCfu(uUNA)ggucUfcUfuCfacu*c*g	1751
AV06972	AV06972-SS	c*a*gugaagAfgAfcCfaagaug*a*a	1451	AV06972-AS	u*Uf*caUfc(uUNA)ugguCfuCfuUfcac*u*g	1752
AV06973	AV06973-SS	g*g*aagagaCfcAfaGfaugaag*u*a	1452	AV06973-AS	u*Af*cuUfc(aUNA)ucuuGfgUfcUfcuu*c*c	1753
AV06974	AV06974-SS	g*a*gagaccAfaGfaUfgaaguu*u*a	1453	AV06974-AS	u*Af*aaCfu(uUNA)caucUfuGfgUfcuc*u*c	1754
AV06975	AV06975-SS	g*g*agaccaAfgAfuGfaaguuu*c*a	1454	AV06975-AS	u*Gf*aaAfc(uUNA)ucauCfuUfgGfucu*c*c	1755
AV06976	AV06976-SS	c*a*ccaagaUfgAfaGfuuuccc*a*a	1455	AV06976-AS	u*Uf*ggGfa(aUNA)acuuCfaUfcUfugg*u*g	1756
AV06977	AV06977-SS	c*a*cuggagGfcAfuCfagauuc*c*a	1456	AV06977-AS	u*Gf*gaAfu(cUNA)ugauGfcCfuCfcag*u*g	1757
AV06978	AV06978-SS	g*a*acaaccAfcCfuGfgcaaua*u*a	1457	AV06978-AS	u*Af*uaUfu(gUNA)ccagGfuGfgUfugu*u*c	1758
AV06979	AV06979-SS	g*a*caaccaCfcUfgGfcaauau*g*a	1458	AV06979-AS	u*Cf*auAfu(uUNA)gccaGfgUfgGfuug*u*c	1759
AV06980	AV06980-SS	g*c*aaccacCfuGfgCfaauaug*a*a	1459	AV06980-AS	u*Uf*caUfa(uUNA)ugccAfgGfuGfguu*g*c	1760
AV06981	AV06981-SS	g*c*cuggcaAfuAfuGfacucac*u*a	1460	AV06981-AS	u*Af*guGfa(gUNA)ucauAfuUfgCfcag*g*c	1761
AV06982	AV06982-SS	g*c*uggcaaUfaUfgAfcucacu*u*a	1461	AV06982-AS	u*Af*agUfg(aUNA)gucaUfaUfuGfcca*g*c	1762

AV06983	AV06983-SS	g*u*ggcaauAfuGfaCfucacuu*g*a	1462	AV06983-AS	u*Cf*aaGfu(gUNA)agucAfuAfuUfgcc*a*c	1763
AV06984	AV06984-SS	c*g*caauauGfaCfuCfacuuga*c*a	1463	AV06984-AS	u*Gf*ucAfa(gUNA)ugagUfcAfuAfuug*c*g	1764
AV06985	AV06985-SS	g*c*aaauggGfcAfcUfuucuug*u*a	1464	AV06985-AS	u*Af*caAfg(aUNA)aaguGfcCfcAfuuu*g*c	1765
AV06986	AV06986-SS	g*a*aaugggCfaCfuUfucuugu*c*a	1465	AV06986-AS	u*Gf*acAfa(gUNA)aaagUfgCfcCfauu*u*c	1766
AV06987	AV06987-SS	g*a*augggcAfcUfuUfcuuguc*u*a	1466	AV06987-AS	u*Af*gaCfa(aUNA)gaaaGfuGfcCfcau*u*c	1767
AV06988	AV06988-SS	g*a*ugggcaCfuUfuCfuugucu*g*a	1467	AV06988-AS	u*Cf*agAfc(aUNA)agaaAfgUfgCfcca*u*c	1768
AV06989	AV06989-SS	g*u*gggcacUfuUfcUfugucug*a*a	1468	AV06989-AS	u*Uf*caGfa(cUNA)aagaAfaGfuGfccc*a*c	1769
AV06990	AV06990-SS	c*g*gcacuuUfcUfuGfucugag*a*a	1469	AV06990-AS	u*Uf*cuCfa(gUNA)acaaGfaAfaGfugc*c*g	1770
AV06991	AV06991-SS	c*c*acuuucUfuGfuCfugagac*u*a	1470	AV06991-AS	u*Af*guCfu(cUNA)agacAfaGfaAfagu*g*g	1771
AV06992	AV06992-SS	g*c*uuucuuGfuCfuGfagacuc*u*a	1471	AV06992-AS	u*Af*gaGfu(cUNA)ucagAfcAfaGfaaa*g*c	1772
AV06993	AV06993-SS	g*c*cagguuGfgCfuGfaugugu*u*a	1472	AV06993-AS	u*Af*acAfc(aUNA)ucagCfcAfaCfcug*g*c	1773
AV06994	AV06994-SS	g*a*cuuagcCfuCfuCfccaaga*u*a	1473	AV06994-AS	u*Af*ucUfu(gUNA)ggagAfgGfcUfaag*u*c	1774
AV06995	AV06995-SS	g*c*ucucccAfaGfaUfgagaaa*g*a	1474	AV06995-AS	u*Cf*uuUfc(uUNA)caucUfuGfgGfaga*g*c	1775
AV06996	AV06996-SS	g*u*cucccaAfgAfuGfagaaag*u*a	1475	AV06996-AS	u*Af*cuUfu(cUNA)ucauCfuUfgGfgag*a*c	1776
AV06997	AV06997-SS	g*c*ucccaaGfaUfgAfgaaagu*c*a	1476	AV06997-AS	u*Gf*acUfu(uUNA)cucaUfcUfuGfgga*g*c	1777
AV06998	AV06998-SS	c*a*ggaggaAfgCfaGfauagau*g*a	1477	AV06998-AS	u*Cf*auCfu(aUNA)ucugCfuUfcCfucc*u*g	1778
AV06999	AV06999-SS	c*g*aggaagCfaGfaUfagaugg*u*a	1478	AV06999-AS	u*Af*ccAfu(cUNA)uaucUfgCfuUfccu*c*g	1779
AV07000	AV07000-SS	g*a*gaaacaGfgAfgUfcaggaa*a*a	1479	AV07000-AS	u*Uf*uuCfc(uUNA)gacuCfcUfgUfuuc*u*c	1780
AV07001	AV07001-SS	c*a*ggcacuAfaGfcCfuaagaa*g*a	1480	AV07001-AS	u*Cf*uuCfu(uUNA)aggcUfuAfgUfgcc*u*g	1781
AV07002	AV07002-SS	c*g*cacuaaGfcCfuAfagaagu*u*a	1481	AV07002-AS	u*Af*acUfu(cUNA)uuagGfcUfuAfgug*c*g	1782
AV07003	AV07003-SS	c*c*acuaagCfcUfaAfgaaguu*c*a	1482	AV07003-AS	u*Gf*aaCfu(uUNA)cuuaGfgCfuUfagu*g*g	1783
AV07004	AV07004-SS	g*a*guucccUfgGfuUfuuuccc*a*a	1483	AV07004-AS	u*Uf*ggGfa(aUNA)aaacCfaGfgGfaac*u*c	1784
AV07005	AV07005-SS	g*a*cugggaGfaCfaAfgcauuu*a*a	1484	AV07005-AS	u*Uf*aaAfu(gUNA)cuugUfcUfcCfcag*u*c	1785
AV07006	AV07006-SS	c*g*gagacaAfgCfaUfuuauac*u*a	1485	AV07006-AS	u*Af*guAfu(aUNA)aaugCfuUfgUfcuc*c*g	1786
AV07007	AV07007-SS	c*g*agacaaGfcAfuUfuauacu*u*a	1486	AV07007-AS	u*Af*agUfa(uUNA)aaauGfcUfuGfucu*c*g	1787
AV07008	AV07008-SS	g*g*acaagcAfuUfuAfuacuuu*c*a	1487	AV07008-AS	u*Gf*aaAfg(uUNA)auaaAfuGfcUfugu*c*c	1788
AV07009	AV07009-SS	c*a*caagcaUfuUfaUfacuuuc*u*a	1488	AV07009-AS	u*Af*gaAfa(gUNA)uauaAfaUfgCfuug*u*g	1789
AV07010	AV07010-SS	g*c*aagcauUfuAfuAfcuuucu*u*a	1489	AV07010-AS	u*Af*agAfa(aUNA)guauAfaAfuGfcuu*g*c	1790
AV07011	AV07011-SS	g*a*ggcgccCfaCfuAfauuuuu*g*a	1490	AV07011-AS	u*Cf*aaAfa(aUNA)uuagUfgGfgCfgcc*u*c	1791

AV07012	AV07012-SS	g*g*aaacgaGfgUfuUfcaacau*g*a	1491	AV07012-AS	u*Cf*auGfu(uUNA)gaaaCfcUfcGfuuu*c*c	1792
AV07013	AV07013-SS	g*g*ccuggcUfuAfuAfcuuucu*u*a	1492	AV07013-AS	u*Af*agAfa(aUNA)guauAfaGfcCfagg*c*c	1793
AV07014	AV07014-SS	c*c*cuggcuUfaUfaCfuuucuu*a*a	1493	AV07014-AS	u*Uf*aaGfa(aUNA)aguaUfaAfgCfcag*g*g	1794
AV07015	AV07015-SS	g*u*ggcuuaUfaCfuUfucuuaa*u*a	1494	AV07015-AS	u*Af*uuAfa(gUNA)aaagUfaUfaAfgcc*a*c	1795
AV07016	AV07016-SS	g*g*gcuuauAfcUfuUfcuuaau*a*a	1495	AV07016-AS	u*Uf*auUfa(aUNA)gaaaGfuAfuAfagc*c*c	1796
AV07017	AV07017-SS	c*g*cuuauaCfuUfuCfuuaaua*a*a	1496	AV07017-AS	u*Uf*uaUfu(aUNA)agaaAfgUfaUfaag*c*g	1797
AV07018	AV07018-SS	g*u*uauacuUfuCfuUfaauaaa*a*a	1497	AV07018-AS	u*Uf*uuUfa(uUNA)uaagAfaAfgUfaua*a*c	1798
AV07019	AV07019-SS	g*a*cuuucuUfaAfuAfaaaagg*a*a	1498	AV07019-AS	u*Uf*ccUfu(uUNA)uuauUfaAfgAfaag*u*c	1799
AV07020	AV07020-SS	g*u*uucuuaAfuAfaAfaaggag*a*a	1499	AV07020-AS	u*Uf*cuCfc(uUNA)uuuuAfuUfaAfgaa*a*c	1800
AV07021	AV07021-SS	g*u*ucuuaaUfaAfaAfaggaga*a*a	1500	AV07021-AS	u*Uf*ucUfc(cUNA)uuuuUfaUfuAfaga*a*c	1801
AV07022	AV07022-SS	g*u*cuuaauAfaAfaAfggagaaa*a*a	1501	AV07022-AS	u*Uf*uuCfu(cUNA)cuuuUfuAfuUfaag*a*c	1802
AV07023	AV07023-SS	g*c*uuaauaAfaAfaGfgagaaa*g*a	1502	AV07023-AS	u*Cf*uuUfc(uUNA)ccuuUfuUfaUfuaa*g*c	1803
AV07024	AV07024-SS	g*g*acucacUfuGfaCfccccuau*g*a	1503	AV07024-AS	u*Cf*auAfg(gUNA)ggucAfaGfuGfagu*c*c	1804
AV07025	AV07025-SS	c*a*cucacuUfgAfcCfccuaug*g*a	1504	AV07025-AS	u*Cf*caUfa(gUNA)ggguCfaAfgUfgag*u*g	1805
AV07026	AV07026-SS	c*g*acccaaAfuGfgGfcacuuu*c*a	1505	AV07026-AS	u*Gf*aaAfg(uUNA)gcccAfuUfuGfggu*c*g	1806
AV07027	AV07027-SS	c*g*cacuuuCfuUfgUfcugaga*c*a	1506	AV07027-AS	u*Gf*ucUfc(aUNA)gacaAfgAfaAfgug*c*g	1807
AV07028	AV07028-SS	g*a*cuuucuUfgUfcUfgagacu*c*a	1507	AV07028-AS	u*Gf*agUfc(uUNA)cagaCfaAfgAfaag*u*c	1808
AV07029	AV07029-SS	g*u*ucuuguCfuGfaGfacucug*g*a	1508	AV07029-AS	u*Cf*caGfa(gUNA)ucucAfgAfcAfaga*a*c	1809
AV07030	AV07030-SS	g*c*uugucuGfaGfaCfucuggc*u*a	1509	AV07030-AS	u*Af*gcCfa(gUNA)agucUfcAfgAfcaa*g*c	1810
AV07031	AV07031-SS	g*u*ugucugAfgAfcUfcuggcu*u*a	1510	AV07031-AS	u*Af*agCfc(aUNA)gaguCfuCfaGfaca*a*c	1811
AV07032	AV07032-SS	g*c*cugguuUfuUfcCfcagggg*a*a	1511	AV07032-AS	u*Uf*ccCfc(uUNA)gggaAfaAfaCfcag*g*c	1812
AV07033	AV07033-SS	g*c*ugguuuUfuCfcCfaggggga*c*a	1512	AV07033-AS	u*Gf*ucCfc(cUNA)ugggAfaAfaAfcca*g*c	1813
AV07034	AV07034-SS	g*u*gguuuuUfcCfcAfggggac*a*a	1513	AV07034-AS	u*Uf*guCfc(cUNA)cuggGfaAfaAfacc*a*c	1814
AV07035	AV07035-SS	g*g*guuuuuCfcCfaGfggggaca*g*a	1514	AV07035-AS	u*Cf*ugUfc(cUNA)ccugGfgAfaAfaac*c*c	1815
AV07036	AV07036-SS	g*u*cccaggGfgAfcAfggaccc*a*a	1515	AV07036-AS	u*Uf*ggGfu(cUNA)cuguCfcCfcUfggg*a*c	1816
AV07037	AV07037-SS	g*g*gggacaGfgAfcCfcacugg*g*a	1516	AV07037-AS	u*Cf*ccAfg(uUNA)ggguCfcUfgUfccc*c*c	1817
AV07038	AV07038-SS	c*a*caggacCfcAfcUfgggaga*c*a	1517	AV07038-AS	u*Gf*ucUfc(cUNA)caguGfgGfuCfcug*u*g	1818
AV07039	AV07039-SS	g*c*aggaccCfaCfuGfggagac*a*a	1518	AV07039-AS	u*Uf*guCfu(cUNA)ccagUfgGfgUfccu*g*c	1819
AV07040	AV07040-SS	g*g*gacccaCfuGfgGfagacaa*g*a	1519	AV07040-AS	u*Cf*uuGfu(cUNA)ucccAfgUfgGfguc*c*c	1820

AV07041	AV07041-SS	c*a*cccacuGfgGfaGfacaagc*a*a	1520	AV07041-AS	u*Uf*gcUfu(gUNA)ucucCfcAfgUfggg*u*g	1821
AV07042	AV07042-SS	g*c*acugggAfgAfcAfagcauu*u*a	1521	AV07042-AS	u*Af*aaUfg(cUNA)uuguCfuCfcCfagu*g*c	1822
AV07043	AV07043-SS	g*c*ugggagAfcAfaGfcauuua*u*a	1522	AV07043-AS	u*Af*uaAfa(uUNA)gcuuGfuCfuCfcca*g*c	1823
AV07044	AV07044-SS	g*g*ggagacAfaGfcAfuuuaua*c*a	1523	AV07044-AS	u*Gf*uaUfa(aUNA)augcUfuGfuCfucc*c*c	1824

【0118】 表 3 示出了本發明的某些經化學修飾的 INHBE RNAi 藥劑反義鏈序列和有義鏈序列。在本發明的方法的一些實施方案中，將表 3 所示的 RNAi 藥劑施用於細胞和/或受試者。在本發明的方法的一些實施方案中，將具有表 3 所示的多核苷酸序列的 RNAi 藥劑施用於受試者。在本發明的一些實施方案中，施用於受試者的 RNAi 藥劑包含表 3 第一列的某一行中標識的雙鏈體，並且包含表 3 第三列和第六列的同一行中的有義鏈序列和反義鏈序列分別所示的序列修飾和/或遞送化合物。這些序列用於本文別處所述的某些體內測試研究。在本發明的方法的一些實施方案中，表 3 所示的序列可與遞送化合物連接（本文也稱為“綴合”），該遞送化合物的非限制性示例是含 GalNAc 的化合物，其中遞送化合物在表 3 第三列中的有義鏈上被標識為“GLX-n”。如本文所用，“GLX-n”用於表示“GLS-n*”遞送化合物或“GLO-n”遞送化合物（“X”可以是“S”或“O”），並且 GLX-0 可以是可在合成期間與寡核苷酸的 3'-端連接的“GLS-n*”遞送化合物和“GLO-n”遞送化合物中的任一者。如本文所用並且如表 3 所示，用於表示所連接的含 GalNAc 的化合物的“GLX-n”是化合物 GLS-1*、GLS-2*、GLS-3*、GLS-4*、GLS-5*、GLS-6*、GLS-7*、GLS-8*、GLS-9*、GLS-10*、GLS-11*、GLS-12*、GLS-13*、GLS-14*、GLS-15*、GLS-16*、GLO-1、GLO-2、GLO-3、GLO-4、GLO-5、GLO-6、GLO-7、GLO-8、GLO-

9、GLO-10、GLO-11、GLO-12、GLO-13、GLO-14、GLO-15 和 GLO-16 的任一者，這些化合物中的每一者的結構均提供於本文別處。本領域技術人員能夠製備和使用本發明的 dsRNA 化合物，其中所連接的遞送化合物是 GLS-1*、GLS-2*、GLS-3*、GLS-4*、GLS-5*、GLS-6*、GLS-7*、GLS-8*、GLS-9*、GLS-10*、GLS-11*、GLS-12*、GLS-13*、GLS-14*、GLS-15*、GLS-16*、GLO-1、GLO-2、GLO-3、GLO-4、GLO-5、GLO-6、GLO-7、GLO-8、GLO-9、GLO-10、GLO-11、GLO-12、GLO-13、GLO-14、GLO-15 和 GLO-16 中的一者。表 3 的第一列提供了分配給該表的某一行中的有義序列和反義序列的雙鏈體的雙鏈體 AD#。例如，雙鏈體 AD# AD00917 是有義鏈 SEQ ID NO: 765 和反義鏈 SEQ ID NO: 808 的雙鏈體。表 3 中的每一行提供了有義鏈和反義鏈，並公開了具有所示有義鏈和反義鏈的雙鏈體。表 3 第二列中的“有義鏈 SS#”是同一行中第 3 列所示的有義序列（包括修飾）的所分配的標識符。表 3 第五列中的“反義鏈 AS#”是第六列所示的反義序列（包括修飾）的所分配的標識符。某些連接的含 GalNAc 的“GLO-n”或“GLS-n*”化合物的標識符被顯示為 GLS-5*、GLS-15*或 GLX-0，並且應當理解，另一種“GLO-n”或“GLS-n*”化合物可取代顯示為 GLO-0 的化合物，其中所得化合物包括在本發明的方法和/或組合物的實施方案中。

【0119】 表 3 提供了經化學修飾的 INHBE RNAi 藥劑反義鏈序列和有義鏈序列。所有序列均以 5'至 3'示出。這些序列用於本文別處所述的某些體內測試研究。用於體內研究的遞送分子在每條有義鏈的 3'-端或 5'-端處被表示為“GLO-n”或“GLS-n*”。

雙鏈體 AD#	有義鏈 SS#	有義序列	SEQ ID NO	反義鏈 AS#	反義序列	SEQ ID NO
AD00917	AD00917-SS	(GLS-15*)(invab*)gacucuuuGfcUfuGfaggaucu*a*(invab)	765	AD00917-AS	u*Af*gaucCfucaaGfcAfaAfgag*u*c	808
AD00918	AD00918-SS	(GLS-15*)(invab*)gguccugaAfaCfuGfcaacuag*a*(invab)	766	AD00918-AS	u*Cf*uaguUfgcagUfuUfcAfgga*c*c	809
AD00919	AD00919-SS	(GLS-15*)(invab*)guuccuagAfgCfuUfaagaucc*a*(invab)	767	AD00919-AS	u*Gf*gaucUfuaagCfuCfuAfgga*a*c	810
AD00920	AD00920-SS	(GLS-15*)(invab*)guggaucaUfaAfuGfgcaaugu*a*(invab)	768	AD00920-AS	u*Af*cauuGfccauUfaUfgAfucc*a*c	811
AD00921	AD00921-SS	(GLS-15*)(invab*)gauaauggCfaAfuGfuggucaa*a*(invab)	769	AD00921-AS	u*Uf*ugacCfacauUfgCfcAfuua*u*c	812
AD00922	AD00922-SS	(GLS-15*)(invab*)gaacaaccAfcCfuGfgcaauau*a*(invab)	770	AD00922-AS	u*Af*uauuGfccagGfuGfgUfugu*u*c	813
AD00923	AD00923-SS	(GLS-15*)(invab*)cgcaauauGfaCfuCfacuugac*a*(invab)	771	AD00923-AS	u*Gf*ucaaGfugagUfcAfuAfuug*c*g	814
AD00924	AD00924-SS	(GLS-15*)(invab*)ccacuuucUfuGfuCfugagacu*a*(invab)	772	AD00924-AS	u*Af*gucuCfagacAfaGfaAfagu*g*g	815
AD00925	AD00925-SS	(GLS-15*)(invab*)gucucccaAfgAfuGfagaaagu*a*(invab)	773	AD00925-AS	u*Af*cuuuCfucauCfuUfgGfgag*a*c	816
AD00926	AD00926-SS	(GLS-15*)(invab*)cgagacaaGfcAfuUfuauacuu*a*(invab)	774	AD00926-AS	u*Af*aguaUfaaauGfcUfuGfucu*c*g	817
AD00927	AD00927-SS	(GLS-15*)(invab*)ggacaagcAfuUfuAfuacuuuc*a*(invab)	775	AD00927-AS	u*Gf*aaagUfauaaAfuGfcUfugu*c*c	818
AD00963	AD00963-SS	(GLS-15*)(invab*)guagccaaGfcAfgCfaaauccu*a*(invab)	776	AD00963-AS	u*Af*ggauUfugcuGfcUfuGfgcu*a*c	819
AD00964	AD00964-SS	(GLS-15*)(invab*)gcagucguCfcCfaGfaauaacu*a*(invab)	777	AD00964-AS	u*Af*guuaUfucugGfgAfcGfacu*g*c	820
AD00965	AD00965-SS	(GLS-15*)(invab*)gagacuccAfcUfuCfagccuac*a*(invab)	778	AD00965-AS	u*Gf*uaGfg(cUNA)ugaaGfuGfgAfguc*u*c	821
AD00966	AD00966-SS	(GLS-15*)(invab*)gccuggcaCfuCfuUfugcuuga*a*(invab)	779	AD00966-AS	u*Uf*caagCfaaagAfgUfgCfcag*g*c	822
AD00967	AD00967-SS	(GLS-15*)(invab*)ccacucuuUfgCfuUfgaggauc*a*(invab)	780	AD00967-AS	u*Gf*auCfc(uUNA)caagCfaAfaGfagu*g*g	823
AD00968	AD00968-SS	(GLS-15*)(invab*)gugcuugaGfgAfuCfuuccgau*a*(invab)	781	AD00968-AS	u*Af*ucggAfagauCfcUfcAfagc*a*c	824
AD00969	AD00969-SS	(GLS-15*)(invab*)gacagcacAfgUfuAfcuggaca*a*(invab)	782	AD00969-AS	u*Uf*guCfc(aUNA)guaaCfuGfuGfcug*u*c	825
AD00	AD009	(GLS-	783	AD0097	u*Gf*gaAfg(uUNA)cuac	826

970	70-SS	15*)(invab*)ggaccauuAfcGfuAfgacuucc*a*(invab)		0-AS	GfuAfaUfggu*c*c	
AD00971	AD00971-SS	(GLS-15*)(invab*)gaauggcaAfuGfuGfgucaaga*a*(invab)	784	AD00971-AS	u*Uf*cuugAfccacAfuUfgCfcau*u*c	827
AD00972	AD00972-SS	(GLS-15*)(invab*)cagugaagAfgAfcCfaagauga*a*(invab)	785	AD00972-AS	u*Uf*caucUfugguCfuCfuUfcac*u*g	828
AD00973	AD00973-SS	(GLS-15*)(invab*)ggaagagaCfcAfaGfaugaagu*a*(invab)	786	AD00973-AS	u*Af*cuucAfucuuGfgUfcUfcuu*c*c	829
AD00974	AD00974-SS	(GLS-15*)(invab*)ggagaccaAfgAfuGfaaguuuc*a*(invab)	787	AD00974-AS	u*Gf*aaacUfucauCfuUfgGfucu*c*c	830
AD00975	AD00975-SS	(GLS-15*)(invab*)gccuggcaAfuAfuGfacucacu*a*(invab)	788	AD00975-AS	u*Af*gugaGfucauAfuUfgCfcag*g*c	831
AD00976	AD00976-SS	(GLS-15*)(invab*)gcuggcaaUfaUfgAfcucacuu*a*(invab)	789	AD00976-AS	u*Af*agugAfgucaUfaUfuGfcca*g*c	832
AD00977	AD00977-SS	(GLS-15*)(invab*)gcaaauggGfcAfcUfuucuugu*a*(invab)	790	AD00977-AS	u*Af*caagAfaaguGfcCfcAfuuu*g*c	833
AD00978	AD00978-SS	(GLS-15*)(invab*)gaaugggcAfcUfuUfcuugucu*a*(invab)	791	AD00978-AS	u*Af*gacaAfgaaaGfuGfcCfcau*u*c	834
AD00979	AD00979-SS	(GLS-15*)(invab*)gcuuucuuGfuCfuGfagacucu*a*(invab)	792	AD00979-AS	u*Af*gaguCfucagAfcAfaGfaaa*g*c	835
AD00980	AD00980-SS	(GLS-15*)(invab*)guauuccaGfgUfuGfgcugaug*a*(invab)	793	AD00980-AS	u*Cf*auCfa(gUNA)ccaaCfcUfgGfaau*a*c	836
AD00981	AD00981-SS	(GLS-15*)(invab*)cacaagcaUfuUfaUfacuuucu*a*(invab)	794	AD00981-AS	u*Af*gaaaGfuauaAfaUfgCfuug*u*g	837
AD00982	AD00982-SS	(GLS-15*)(invab*)cccuggcuUfaUfaCfuuucuua*a*(invab)	795	AD00982-AS	u*Uf*aagaAfaguaUfaAfgCfcag*g*g	838
AD00983	AD00983-SS	(GLS-15*)(invab*)guggcuuaUfaCfuUfucuuaau*a*(invab)	796	AD00983-AS	u*Af*uuaaGfaaagUfaUfaAfgcc*a*c	839
AD00984	AD00984-SS	(GLS-15*)(invab*)gggcuuauAfcUfuUfcuuaaua*a*(invab)	797	AD00984-AS	u*Uf*auuaAfgaaaGfuAfuAfagc*c*c	840
AD00985	AD00985-SS	(GLS-15*)(invab*)cgcuuauaCfuUfuCfuuaauaa*a*(invab)	798	AD00985-AS	u*Uf*uauuAfagaaAfgUfaUfaag*c*g	841
AD00986	AD00986-SS	(GLS-15*)(invab*)guuucuuaAfuAfaAfaaggaga*a*(invab)	799	AD00986-AS	u*Uf*cuccUfuuuuAfuUfaAfgaa*a*c	842
AD00987	AD00987-SS	(GLS-15*)(invab*)guucuuaaUfaAfaAfaggagaa*a*(invab)	800	AD00987-AS	u*Uf*ucucCfuuuuUfaUfuAfaga*a*c	843
AD01272	AD01272-SS	(GLS-15*)(imann*)gaaaugggCfaCfuUfucuuguc*a*(imann)	801	AD01272-AS	u*Gf*acaaGfaaaGfugCfcCfauu*u*c	844
AD01273	AD01273-SS	(GLS-15*)(imann*)gaugggcaCfuUfuC	802	AD01273-AS	u*Cf*agacAfagaAfagUfgCfcca*u*c	845

		fuugucug* a*(imann)				
AD01274	AD01274-SS	(GLS-15*)(imann*)gacugggaGfaCfaAfgcauuua*a*(imann)	803	AD01274-AS	u*Uf*aaauGfcuuGfucUfcCfcag*u*c	846
AD01275	AD01275-SS	(GLS-15*)(imann*)cggagacaAfgCfaUfuuauacu*a*(imann)	804	AD01275-AS	u*Af*guauAfaauGfcuUfgUfcuc*c*g	847
AD01276	AD01276-SS	(GLS-15*)(imann*)gcaagcauUfuAfuAfcuuucuu*a*(imann)	805	AD01276-AS	u*Af*agaaAfguaUfaaAfuGfcuu*g*c	848
AD01277	AD01277-SS	(GLS-15*)(imann*)ggccuggcUfuAfuAfcuuucuu* a*(imann)	806	AD01277-AS	u*Af*agaaAfguaUfaaGfcCfagg*c*c	849
AD01588	AD01588-SS	a*c*cagucgUfCfCfcagaauaacu(L96)	807	AD01588-AS	a*(dG*)uu(dA)u(dT)cugg(dG)aCfgacuggu*c*u	850
AD00974-1	AD00974-1-SS	(GLS-15*)g*gagaccaAfgAfuGfaaguuuc*a*(invab)	1825	AD00974-1-AS	u*Gf*aaacUfucauCfuUfgGfucu*c*c	1880
AD00926-1	AD00926-1-SS	(GLS-15*)c*gagacaaGfcAfuUfuauacuu*a*(invab)	1826	AD00926-1-AS	u*Af*aguaUfaaauGfcUfuGfucu*c*g	1881
AD00927-1	AD00927-1-SS	(GLS-15*)g*gacaagcAfuUfuAfuacuuuc*a*(invab)	1827	AD00927-1-AS	u*Gf*aaagUfauaaAfuGfcUfugu*c*c	1882
AD00964-1	AD00964-1-SS	(GLS-15*)g*cagucguCfcCfaGfaauaacu*a*(invab)	1828	AD00964-1-AS	u*Af*guuaUfucugGfgAfcGfacu*g*c	1883
AD02406	AD02406-SS	(GLS-15*)(invab*)gacuuuucAfcCfuGfuccacuc*a*(invab)	1829	AD02406-AS	u*Gf*agUfg(gUNA)acagGfuGfaAfaag*u*c	1884
AD02407	AD02407-SS	(GLS-15*)(invab*)gccacccuUfcCfuGfgcacucu*a*(invab)	1830	AD02407-AS	u*Af*gaGfu(gUNA)ccagGfaAfgGfgug*g*c	1885
AD02408	AD02408-SS	(GLS-15*)(invab*)cgugagaaGfuCfuGfguguccu*a*(invab)	1831	AD02408-AS	u*Af*ggAfc(aUNA)ccagAfcUfuCfuca*c*g	1886
AD02409	AD02409-SS	(GLS-15*)(invab*)cagaagucUfgGfuGfuccugaa*a*(invab)	1832	AD02409-AS	u*Uf*ucagGfacacCfaGfaCfuuc*u*g	1887
AD02410	AD02410-SS	(GLS-15*)(invab*)caagucugGfuGfuCfcugaaac*a*(invab)	1833	AD02410-AS	u*Gf*uuucAfggacAfcCfaGfacu*u*g	1888
AD02411	AD02411-SS	(GLS-15*)(invab*)cagcuuaaGfaUfcCfgagccaa*a*(invab)	1834	AD02411-AS	u*Uf*ugGfc(uUNA)cggaUfcUfuAfagc*u*g	1889
AD02412	AD02412-SS	(GLS-15*)(invab*)ccuuaagaUfcCfgAfgccaaug*a*(invab)	1835	AD02412-AS	u*Cf*auUfg(gUNA)cucgGfaUfcUfuaa*g*g	1890
AD02413	AD02413-SS	(GLS-15*)(invab*)guuacguaGfaCfuUfccaggaa*a*(invab)	1836	AD02413-AS	u*Uf*ucCfu(gUNA)gaagUfcUfaCfgua*a*c	1891
AD02414	AD02414-SS	(GLS-15*)(invab*)cggguaccAfgCfuGfaauuacu*a*(invab)	1837	AD02414-AS	u*Af*guaaUfucagCfuGfgUfacc*c*g	1892
AD02415	AD02415-SS	(GLS-15*)(invab*)guggagugAfaGfaGfaccaaga*a*(invab)	1838	AD02415-AS	u*Uf*cuugGfucucUfuCfaCfucc*a*c	1893
AD02	AD024	(GLS-	1839	AD0241	u*Gf*gaauCfugauGfcCfu	1894

416	16-SS	15*)(invab*)cacuggagGfcAfuCfagauucc*a*(invab)		6-AS	Cfcag*u*g	
AD02417	AD02417-SS	(GLS-15*)(invab*)gaauaugaCfuCfaCfuugaccc*a*(invab)	1840	AD02417-AS	u*Gf*ggUfc(aUNA)agugAfgUfcAfuau*u*c	1895
AD02418	AD02418-SS	(GLS-15*)(invab*)gaugacucAfcUfuGfaccccua*a*(invab)	1841	AD02418-AS	u*Uf*agGfg(gUNA)ucaaGfuGfaGfuca*u*c	1896
AD02419	AD02419-SS	(GLS-15*)(invab*)cuuucuucUfaAfaGfgggucua*a*(invab)	1842	AD02419-AS	u*Uf*agAfc(cUNA)ccuuUfaGfaAfgaa*a*g	1897
AD02420	AD02420-SS	(GLS-15*)(invab*)gacuuagcCfuCfuCfccaagau*a*(invab)	1843	AD02420-AS	u*Af*ucuuGfggagAfgGfcUfaag*u*c	1898
AD02421	AD02421-SS	(GLS-15*)(invab*)gcucccaaGfaUfgAfgaaaguc*a*(invab)	1844	AD02421-AS	u*Gf*acuuUfcucaUfcUfuGfgga*g*c	1899
AD02422	AD02422-SS	(GLS-15*)(invab*)gagaaacaGfgAfgUfcaggaaa*a*(invab)	1845	AD02422-AS	u*Uf*uuccUfgacuCfcUfgUfuuc*u*c	1900
AD02423	AD02423-SS	(GLS-15*)(invab*)cccuaagaAfgUfuCfccugguu*a*(invab)	1846	AD02423-AS	u*Af*acCfa(gUNA)ggaaCfuUfcUfuag*g*g	1901
AD02424	AD02424-SS	(GLS-15*)(invab*)ggaaacgaGfgUfuUfcaacaug*a*(invab)	1847	AD02424-AS	u*Cf*auguUfgaaaCfcUfcGfuuu*c*c	1902
AD02425	AD02425-SS	(GLS-15*)(invab*)guuauacuUfuCfuUfaauaaaa*a*(invab)	1848	AD02425-AS	u*Uf*uuuaUfuaagAfaAfgUfaua*a*c	1903
AD02426	AD02426-SS	(GLS-15*)(invab*)gacuuucuUfaAfuAfaaaagga*a*(invab)	1849	AD02426-AS	u*Uf*ccuuUfuuauUfaAfgAfaag*u*c	1904
AD02427	AD02427-SS	(GLS-15*)(invab*)gucuuaauAfaAfaAfggagaaa*a*(invab)	1850	AD02427-AS	u*Uf*uucuCfcuuuUfuAfuUfaag*a*c	1905
AD02428	AD02428-SS	(GLS-15*)(invab*)gcuuaauaAfaAfaGfgagaaag*a*(invab)	1851	AD02428-AS	u*Cf*uuucUfccuuUfuUfaUfuaa*g*c	1906
AD03238	AD03238-SS	(GLS-15*)g*uugucugAfgAfcUfcuggcuu*a*(invab)	1852	AD03238-AS	u*Af*agCfc(aUNA)gaguCfuCfaGfaca*a*c	1907
AD03239	AD03239-SS	(GLS-15*)g*uagccaaGfcAfgCfaaauccu*a*(invab)	1853	AD03239-AS	u*Af*ggAfu(uUNA)ugcuGfcUfuGfgcu*a*c	1908
AD03240	AD03240-SS	(GLS-15*)c*ccuggcuUfaUfaCfuuucuua*a*(invab)	1854	AD03240-AS	u*Uf*aaGfa(aUNA)aguaUfaAfgCfcag*g*g	1909
AD03241	AD03241-SS	(GLS-15*)g*ugcuugaGfgAfuCfuuccgau*a*(invab)	1855	AD03241-AS	u*Af*ucGfg(aUNA)agauCfcUfcAfagc*a*c	1910
AD03242	AD03242-SS	(GLS-15*)g*gagaccaAfgAfuGfaaguuuc*a*(invab)	1856	AD03242-AS	u*Gf*aaAfc(uUNA)ucauCfuUfgGfucu*c*c	1911
AD03243	AD03243-SS	(GLS-15*)g*accuggaUfcAfuAfauggcaa*a*(invab)	1857	AD03243-AS	u*Uf*ugCfc(aUNA)uuauGfaUfcCfagg*u*c	1912
AD03244	AD03244-SS	(GLS-15*)g*agaaacaGfgAfgUfcaggaa	1858	AD03244-AS	u*Uf*uuCfc(uUNA)gacuCfcUfgUfuuc*u*c	1913

		a*a*(invab)				
AD03245	AD03245-SS	(GLS-15*)g*aauggcaAfuGfuGfgucaaga*a*(invab)	1859	AD03245-AS	u*Uf*cuUfg(aUNA)ccacAfuUfgCfcau*u*c	1914
AD03246	AD03246-SS	(GLS-15*)g*cuuucuuGfuCfuGfagacucu*a*(invab)	1860	AD03246-AS	u*Af*gaGfu(cUNA)ucagAfcAfaGfaaa*g*c	1915
AD03247	AD03247-SS	(GLS-15*)g*gaaacgaGfgUfuUfcaacaug*a*(invab)	1861	AD03247-AS	u*Cf*auGfu(uUNA)gaaaCfcUfcGfuuu*c*c	1916
AD03248	AD03248-SS	(GLS-15*)g*augggcaCfuUfuCfuugucug*a*(invab)	1862	AD03248-AS	u*Cf*agAfc(aUNA)agaaAfgUfgCfcca*u*c	1917
AD03249	AD03249-SS	(GLS-15*)g*uccucuaCfcUfgGfaucauaa*a*(invab)	1863	AD03249-AS	u*Uf*uaUfg(aUNA)uccaGfgUfaGfagg*a*c	1918
AD03250	AD03250-SS	(GLS-15*)g*ggaggcaUfcAfgAfuuccuga*a*(invab)	1864	AD03250-AS	u*Uf*caGfg(aUNA)aucuGfaUfgCfcuc*c*c	1919
AD03251	AD03251-SS	(GLS-15*)g*uggagugAfaGfaGfaccaaga*a*(invab)	1865	AD03251-AS	u*Uf*cuUfg(gUNA)ucucUfuCfaCfucc*a*c	1920
AD03252	AD03252-SS	(GLS-15*)c*agacaagCfaUfuUfauacuuu*a*(invab)	1866	AD03252-AS	u*Af*aaGfu(aUNA)uaaaUfgCfuUfguc*u*g	1921
AD03253	AD03253-SS	(GLS-15*)g*ggcuuauAfcUfuUfcuuaaua*a*(invab)	1867	AD03253-AS	u*Uf*auUfa(aUNA)gaaaGfuAfuAfagc*c*c	1922
AD03254	AD03254-SS	(GLS-15*)c*gagacaaGfcAfuUfuauacuu*a*(invab)	1868	AD03254-AS	u*Af*agUfa(uUNA)aaauGfcUfuGfucu*c*g	1923
AD03255	AD03255-SS	(GLS-15*)g*cccaagaUfgAfgAfaagccu*a*(invab)	1869	AD03255-AS	u*Af*ggAfc(uUNA)uucuCfaUfcUfugg*g*c	1924
AD03256	AD03256-SS	(GLS-15*)c*ggagacaAfgCfaUfuuauacu*a*(invab)	1870	AD03256-AS	u*Af*guAfu(aUNA)aaugCfuUfgUfcuc*c*g	1925
AD03257	AD03257-SS	(GLS-15*)g*ccagguuGfgCfuGfaugugu*a*(invab)	1871	AD03257-AS	u*Af*acAfc(aUNA)ucagCfcAfaCfcug*g*c	1926
AD03258	AD03258-SS	(GLS-15*)c*gagugaaGfaGfaCfcaagaug*a*(invab)	1872	AD03258-AS	u*Cf*auCfu(uUNA)ggucUfcUfuCfacu*c*g	1927
AD03259	AD03259-SS	(GLS-15*)g*aagacggAfuGfuGfccagaua*a*(invab)	1873	AD03259-AS	u*Uf*auCfu(gUNA)gcacAfuCfcGfucu*u*c	1928
AD03260	AD03260-SS	(GLS-15*)g*gacuggaGfgCfaUfcagauuc*a*(invab)	1874	AD03260-AS	u*Gf*aaUfc(uUNA)gaugCfcUfcCfagu*c*c	1929
AD03261	AD03261-SS	(GLS-15*)g*aaugggcAfcUfuUfcuugcu*a*(invab)	1875	AD03261-AS	u*Af*gaCfa(aUNA)gaaaGfuGfcCfcau*u*c	1930
AD03262	AD03262-SS	(GLS-15*)c*acaagcaUfuUfaUfacuuuc*a*(invab)	1876	AD03262-AS	u*Af*gaAfa(gUNA)uauaAfaUfgCfuug*u*g	1931
AD03263	AD03263-SS	(GLS-15*)g*ucuaccuGfgAfuCfauaaug*g*a*(invab)	1877	AD03263-AS	u*Cf*caUfu(aUNA)ugauCfcAfgGfuag*a*c	1932

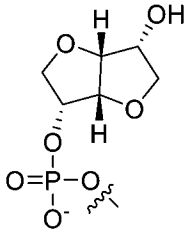
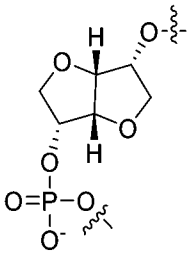
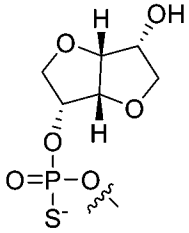
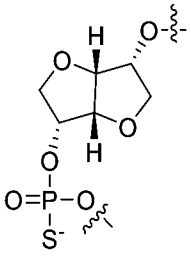
AD03264	AD03264-SS	(GLS-15*)g*auaauggCfaAfuGfuggucaa*a*(invab)	1878	AD03264-AS	u*Uf*ugAfc(cUNA)acauUfgCfcAfuua*u*c	1933
AD03265	AD03265-SS	(GLS-15*)g*cagucguCfcCfaGfaauaacu*a*(invab)	1879	AD03265-AS	u*Af*guUfa(uUNA)ucugGfgAfcGfacu*g*c	1934

L96是指Jayaprakash等人，(2014) J. Am. Chem.Soc., 136, 16958−16961中的化合物GalNAc3。

【0120】

表4：核苷酸序列中使用的核苷酸單體的縮寫表示。應當理解，當這些單體存在於寡核苷酸中時，它們通過5'-3'-磷酸二酯鍵相互連接，並且應當理解，當核苷酸含有2'-氟修飾時，則氟取代親本核苷酸該位置處的羥基（即，它是2'-脫氧-2'-氟核苷酸）。還應當理解，這些縮寫對應於當在3'-末端位置時省略3'-磷酸酯的核苷酸（即，它們是3'-OH）。本領域技術人員應當理解這些縮寫只是標識符號，並且能夠確定含有這些縮寫的核苷酸序列的連接方式。

縮寫	核苷酸
A	腺苷-3'-磷酸酯
C	胞苷-3'-磷酸酯
G	鳥苷-3'-磷酸酯
T	5-甲基尿苷-3'-磷酸酯
U	尿苷-3'-磷酸酯
a	2'-O-甲基腺苷-3'-磷酸酯
c	2'-O-甲基胞苷-3'-磷酸酯
g	2'-O-甲基鳥苷-3'-磷酸酯
t	2'-O-甲基-5-甲基尿苷-3'-磷酸酯
u	2'-O-甲基尿苷-3'-磷酸酯
Af	2'-氟腺苷-3'-磷酸酯
Cf	2'-氟胞苷-3'-磷酸酯
Gf	2'-氟鳥苷-3'-磷酸酯
Tf	2'-氟-5-甲基尿苷-3'-磷酸酯
Uf	2'-氟尿苷-3'-磷酸酯
Af*	2'-氟腺苷-3'-硫代磷酸酯
Cf*	2'-氟胞苷-3'-硫代磷酸酯
Gf*	2'-氟鳥苷-3'-硫代磷酸酯
Tf*	2'-氟-5-甲基尿苷-3'-硫代磷酸酯
Uf*	2'-氟尿苷-3'-硫代磷酸酯
a*	2'-O-甲基腺苷-3'-硫代磷酸酯
c*	2'-O-甲基胞苷-3'-硫代磷酸酯
g*	2'-O-甲基鳥苷-3'-硫代磷酸酯

t*	2'-O-甲基-5-甲基尿苷-3'-硫代磷酸酯
u*	2'-O-甲基尿苷-3'-硫代磷酸酯
aUNA	2',3'-開環-腺苷-3'-磷酸酯
cUNA	2',3'-開環-胞苷-3'-磷酸酯
gUNA	2',3'-開環-鳥苷-3'-磷酸酯
tUNA	2',3'-開環-5-甲基尿苷-3'-磷酸酯
uUNA	2',3'-開環-尿苷-3'-磷酸酯
Vp	乙烯基-膦酸酯
invab	反向無鹼基-5'-磷酸酯。當在鏈的3'端時，經由其3'位置處的取代基（3'-3'鍵）連接到相鄰核苷酸；當在鏈的5'端時，經由其5'位置處的取代基（5'-5'核苷酸間鍵）連接到相鄰核苷酸，還應當理解，當在3'-末端位置時，縮寫對應的invab省略了5'-磷酸(即，它們是 5'-OH)。
invab*	反向無鹼基-5'-硫代磷酸酯。當在鏈的3'端時，經由其3'位置處的取代基（3'-3'鍵）連接到相鄰核苷酸；當在鏈的5'端時，經由其5'位置處的取代基（5'-5'核苷酸間鍵）連接到相鄰核苷酸，還應當理解，當在3'-末端位置發現時，縮寫對應的invab*省略了5'-硫代磷酸(即，它們是5'-OH)。
imann	當異甘露醇殘基在每條鏈的末端時  當異甘露醇殘基在每條鏈的中間時 
imann*	異甘露醇殘基-硫代磷酸酯
	當異甘露醇殘基*在每條鏈的末端時  當異甘露醇殘基*在每條鏈的中間時 
dA	2'-脫氧腺苷-3'-磷酸酯
dG	2'-脫氧鳥苷-3'-磷酸酯
dG*	2'-脫氧鳥苷-3'-硫代磷酸酯
dT	2'-脫氧胸苷-3'-磷酸酯
Ahd	2'-O-十六烷基-腺苷-3'-磷酸酯
Tgn	胸苷-乙二醇核酸（GNA）S-異構體

【0121】 在本發明的某些實施方案中，dsRNA（本文也稱為“雙鏈體”）是表1至表3中的一個表中公開的一種。表1至表3中的每一行公開了包含該表行中的有義鏈序列和反義鏈序列的雙鏈體。除了表1至表3中公開的雙鏈體之外，應當理解，在一些實施方案中，本發明的雙鏈體可包含表1至表3所示的有義序列和反義序列，這些有義序列和反義序列與表1至表3所示的序列相差零、一、二或三個核苷酸。因此，作為非限制性示例，在一些實施方案中，本發明的雙鏈體中的反義鏈可以是與SEQ ID NO: 808、809、822、826或834中的核苷酸相比具有零、一、二或三個不同核苷酸的SEQ ID NO: 808、809、822、826或834。

【0122】 應當理解，本發明的雙鏈體中有義鏈序列和反義鏈序列可以是獨立選擇的。因此，本發明的dsRNA可包含表1至表3中的某一行中公開的雙鏈體的有義鏈和反義鏈。另選地，在本發明的dsRNA中，dsRNA中所選的有義鏈和反義鏈中的一者或兩者可包括表1至表3所示的序列，但有義序列和反義序列中的一者或兩者包含來自親本序列的1、2、3個或更多個核鹼基取代。在一些實施方案中，所選的序列可比它們的親本序列更長或更短。因此，包括在本發明中的dsRNA藥劑可以但不必包含表1至表3中公開為雙鏈體的有義和反義對的精確序列。

【0123】 在一些實施方案中，dsRNA藥劑包含有義鏈和反義鏈，該反義鏈中的核苷酸位置2至18包含與INHBE RNA轉錄本互補的區域，該區域具有與表1至表3中的一個表中列出的反義序列之一相差0、1、2或3個核苷酸的至少15個連續核苷酸，並且任選地包含靶向配體。在一些情況下，與該INHBE RNA轉錄本互補的區域包含與表1至表3中的一個表中列出的反

義序列之一相差不超過3個核苷酸的至少15、16、17、18、或19個連續核苷酸。在本發明的dsRNA藥劑的一些實施方案中，該dsRNA的反義鏈與SEQ ID NO: 1的任一靶區域至少基本上互補，並且提供在表1至表3中的任一個表中。在一些實施方案中，本發明的dsRNA藥劑的反義鏈與SEQ ID NO: 1的任一靶區域完全互補，並且提供在表1至表3的任一個表中。在一些實施方案中，dsRNA藥劑包含表1至表3中的任一個表中示出的有義鏈序列，並且該有義鏈序列與該dsRNA藥劑中的反義鏈序列至少基本上互補。在其他實施方案中，本發明的dsRNA藥劑包含表1至表3中的任一個表中示出的有義鏈序列，並且該有義鏈序列與該dsRNA藥劑中的反義鏈序列完全互補。在一些情況下，本發明的dsRNA藥劑包含表1至表3中的任一個表中示出的反義鏈序列。本發明的dsRNA藥劑的一些實施方案包含表1至表3中的任一個表中公開為雙鏈體的有義序列和反義序列。如本文所述，應當理解本發明的雙鏈體中的有義鏈和反義鏈可以是獨立選擇的。

錯配

【0124】 本領域技術人員已知，就dsRNA的功效而言，錯配是可被容忍的，尤其是錯配位於dsRNA的末端區域內時。某些錯配可被較好容忍，例如就功效而言，具有擺動鹼基對G:U和A:C的錯配可被較好容忍（Du等人，“一種針對所有單核苷酸錯配靶位點處的活性siRNA的沉默效應的系統性分析（A systematic analysis of the silencing effects of an active siRNA at all single-nucleotide mismatched target sites.）”，Nucleic Acids Res.2005 Mar 21;33(5):1671-7.Doi: 10.1093/nar/gki312.Nucleic Acids

Res.2005;33(11):3698）。本發明的方法和化合物的一些實施方案中，INHBE dsRNA藥劑可含有一個或多個與INHBE靶序列的錯配。在一些實施方案中，本發明的INHBE dsRNA藥劑不包含錯配。在某些實施方案中，本發明的INHBE dsRNA藥劑包含不超過1個錯配。在一些實施方案中，本發明的INHBE dsRNA藥劑包含不超過2個錯配。在某些實施方案中，本發明的INHBE dsRNA藥劑包含不超過3個錯配。在本發明的一些實施方案中，INHBE dsRNA藥劑的反義鏈含有與INHBE靶序列的不位於互補區域中心的錯配。在一些實施方案中，INHBE dsRNA藥劑的反義鏈包含位於互補區域的5'端或3'端的一者或兩者的最後5、4、3、2或1個核苷酸內的1、2、3、4個或更多個錯配。本文所述的方法和/或本領域已知的方法可用於測定含有與INHBE靶序列的錯配的INHBE dsRNA藥劑是否有效抑制INHBE基因的表達。

互補

【0125】 如本文所用，除非另有說明，否則術語“互補”在用於描述與第二核苷酸序列（例如，INHBE dsRNA藥劑反義鏈或單鏈反義多核苷酸）相關的第一核苷酸序列（例如，INHBE dsRNA藥劑有義鏈或靶向INHBE mRNA）時，意指包含該第一核苷酸序列的寡核苷酸或多核苷酸在某些條件下與包含該第二核苷酸序列的寡核苷酸或多核苷酸雜交[在哺乳動物生理條件（或體外類似條件）下形成鹼基對氫鍵]並形成雙鏈體或雙螺旋結構的能力。可應用其他條件，諸如在生物體內部可能遇到的生理相關條件。技術人員將能夠根據所雜交的核苷酸的最終應用來確定最適於測試兩個序

列的互補性的一組條件。互補序列包含沃森-克裡克鹼基對或非沃森-克裡克鹼基對，並且包含至少達到滿足上述雜交要求的程度的天然的或經修飾的核苷酸或核苷酸模擬物。序列同一性或互補性不依賴於修飾。

【0126】 例如，在本文所述的INHBE dsRNA內的互補序列包括包含第一核苷酸序列的寡核苷酸或多核苷酸與包含第二核苷酸序列的寡核苷酸或多核苷酸在一個或兩個核苷酸序列的整個長度上的鹼基配對。此類序列在本文中可被稱為相對於彼此“完全互補”。應當理解，在實施方案中，當兩個寡核苷酸被設計成在雜交時形成一個或多個單鏈突出端時，此類突出端在本文中不被視為關於確定互補性的錯配。例如，INHBE dsRNA藥劑包含一個長度為19個核苷酸的寡核苷酸和另一個長度為20個核苷酸的寡核苷酸，其中較長的寡核苷酸包含與較短的寡核苷酸完全互補的具有19個核苷酸的序列，為了本文所述的目的，仍可被稱為“完全互補”。因此，如本文所用，“完全互補”意指第一多核苷酸的連續序列中全部（100%）的鹼基將與第二多核苷酸的連續序列中相同數目的鹼基雜交。這些連續序列可包含第一核苷酸序列或第二核苷酸序列的全部或一部分。

【0127】 如本文所用，術語“基本上互補”意指在核鹼基序列的雜交對中，第一多核苷酸的連續序列中至少約85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%但不是全部的鹼基將與第二多核苷酸的連續序列中相同數目的鹼基雜交。如果兩個序列在雜交時包含一個或多個（例如至少1、2、3、4或5個）錯配鹼基對，形成多達15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30個鹼基對（bp）的雙鏈體，同時保留在與其最終應用最相關的條件下雜交

的能力（例如，經由RISC途徑抑制INHBE基因表達），則術語“基本上互補”可用於指第一序列相對於第二序列。

【0128】 術語“部分互補”在本文中可用於指核鹼基序列的雜交對，其中第一多核苷酸的連續序列中至少75%但不是全部的鹼基將與第二多核苷酸的連續序列中相同數目的鹼基雜交。在一些實施方案中，“部分互補”意指第一多核苷酸的連續序列中至少76%、77%、78%、79%、80%、81%、82%、83%、84%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%的鹼基將與第二多核苷酸的連續序列中相同數目的鹼基雜交。

【0129】 本文所用的術語“互補”、“完全互補”、“基本上互補”和“部分互補”是指INHBE dsRNA藥劑的有義鏈和反義鏈之間、INHBE dsRNA藥劑的反義鏈和靶INHBE mRNA的序列之間、或單鏈反義寡核苷酸和靶INHBE mRNA的序列之間的鹼基匹配。應該理解，術語“INHBE dsRNA藥劑的反義鏈”可以指“INHBE反義多核苷酸藥劑”的相同序列。

【0130】 如本文所用，關於核酸序列所用的術語“基本上相同”或“基本同一性”意指包括與參考序列相比具有至少約85%序列同一性或更高序列同一性（優選至少90%、至少91%、至少92%、至少93%、至少94%、至少95%、至少96%、至少97%、至少98%或至少99%）的序列的核酸序列。通過在比較窗口上比較兩個最佳比對的序列來測定序列同一性的百分比。該百分比的計算方法是：測定兩個序列中出現相同核酸鹼基的位置數，得到匹配位置數，用匹配位置數除以比較窗口中的位置總數，然後將結果乘以100，得到序列同一性的百分比。本文公開的發明涵蓋與本文公開的那些

核苷酸序列（例如，表1至表3中的核苷酸序列）基本上相同的核苷酸序列。在一些實施方案中，本文公開的序列與本文公開的那些序列（例如，表1至表3中的序列）完全相同，或者至少約85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%相同。

【0131】 如本文所用，術語“包含序列的鏈”意指包含由使用標準核苷酸命名法提及的序列描述的核苷酸鏈的寡核苷酸。如本文所用，術語“雙鏈RNA”或“dsRNA”是指包括具有雜交雙鏈體區域的RNA分子或分子複合物的RNAi，該雜交雙鏈體區域包含兩條反向平行且基本上或完全互補的核酸鏈，這兩條核酸鏈相對於靶INHBE RNA被稱為具有“有義”和“反義”取向。雙鏈體區域可具有允許期望的靶INHBE RNA通過RISC途徑進行特異性降解的任何長度，但通常長度範圍為9至30個鹼基對，例如15至30個鹼基對。考慮到雙鏈體具有9至30個鹼基對，該雙鏈體可具有該範圍內的任何長度，例如9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30個鹼基對以及其中的任何子範圍，包括但不限於15至30個鹼基對、15至26個鹼基對、15至23個鹼基對、15至22個鹼基對、15至21個鹼基對、15至20個鹼基對、15至19個鹼基對、15至18個鹼基對、15至17個鹼基對、18至30個鹼基對、18至26個鹼基對、18至23個鹼基對、18至22個鹼基對、18至21個鹼基對、18至20個鹼基對、19至30個鹼基對、19至26個鹼基對、19至23個鹼基對、19至22個鹼基對、19至21個鹼基對、19至20個鹼基對、20至30個鹼基對、20至26個鹼基對、20至25個鹼基對、20至24個鹼基對、20至23個鹼基對、20至22個鹼基對、20至21個鹼基對、21至30個鹼基對、21至26個鹼基對、21至25個鹼基對、21至24個鹼基

對、21至23個鹼基對、或21至22個鹼基對。在細胞中通過用Dicer和類似酶加工而產生的INHBE dsRNA藥劑的長度範圍通常為19至22個鹼基對。INHBE dsDNA藥劑的雙鏈體區域的一條鏈包含與靶INHBE RNA的區域基本上互補的序列。形成雙鏈體結構的兩條鏈可來自具有至少一個自身互補區域的單個RNA分子，或者可由兩個或更多個單獨的RNA分子形成。當雙鏈體區域由單個分子的兩條鏈形成時，該分子可在形成雙鏈體結構的一條鏈的3'-端和相應另一條鏈的5'-端之間具有由單鏈核苷酸鏈分隔的雙鏈體區域（本文中稱為“髮夾環”）。在本發明的一些實施方案中，髮夾環包含至少1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20個或更多個未配對的核苷酸。當INHBE dsRNA藥劑的兩條基本上互補的鏈由單獨的RNA分子組成時，這些分子不必但可以共價連接。當兩條鏈以非髮夾環的方式共價連接時，連接結構被稱為“接頭”。術語“siRNA”在本文中也用於指如本文所述的dsRNA藥劑。

【0132】 在本發明的一些實施方案中，INHBE dsRNA藥劑可包含在dsRNA藥劑的一個或兩個末端處沒有未配對核苷酸或核苷酸類似物的有義序列和反義序列。沒有未配對核苷酸的一端被稱為“平端”並且沒有核苷酸突出端。如果dsRNA藥劑的兩端都是平的，則dsRNA被稱為“平端的”。在本發明的一些實施方案中，dsRNA藥劑的第一端是平的，在一些實施方案中，dsRNA藥劑的第二端是平的，並且在本發明的某些實施方案中，INHBE dsRNA藥劑的兩端都是平的。

【0133】 在本發明的dsRNA藥劑的一些實施方案中，dsRNA不具有一個或兩個平端。在此類情況下，在dsRNA藥劑的鏈的末端處存在至少一

個未配對的核苷酸。例如，當dsRNA的一條鏈的3'-端延伸超過另一條鏈的5'-端時（或者反之亦然），存在核苷酸突出端。dsRNA可包含具有至少1、2、3、4、5、6個或更多個核苷酸的突出端。核苷酸突出端可包含核苷酸/核苷類似物（包括脫氧核苷酸/核苷）或由其組成。應當理解，在一些實施方案中，核苷酸突出端在dsRNA藥劑的有義鏈上，在dsRNA藥劑的反義鏈上，或者在dsRNA藥劑的兩端上，並且突出端的核苷酸可存在於dsRNA的反義鏈或有義鏈的5'端、3'端或兩端上。在本發明的某些實施方案中，突出端中的一個或多個核苷酸被核苷硫代磷酸酯置換。

【0134】 如本文所用，術語“反義鏈”或“引導鏈”是指INHBE dsRNA藥劑的包含與INHBE靶序列基本上互補的區域的鏈。如本文所用，術語“有義鏈”或“過客鏈”指INHBE dsRNA藥劑的包含與INHBE dsRNA藥劑的反義鏈的區域基本上互補的區域的鏈。

修飾

【0135】 在本發明的一些實施方案中，INHBE RNAi藥劑的RNA經化學修飾以增強穩定性和/或一種或多種其他有益特徵。本發明的某些實施方案中的核酸可通過本領域熟知的方法進行合成和/或修飾，例如，描述於“核酸化學實驗室指南（Current protocols in Nucleic Acid Chemistry）”，Beaucage, S. L.等人（編輯），John Wiley & Sons, Inc., New York, N.Y., USA，該文獻以引用方式併入本文。可存在於本發明的INHBE dsRNA藥劑的某些實施方案中的修飾包括，例如，(a)末端修飾，例如5'端修飾（磷酸化、綴合、反向連接等），3'端修飾（綴合、DNA核苷酸、反向連接等），

(b)鹼基修飾，例如用穩定的鹼基、去穩定的鹼基或與擴展的配體庫鹼基配對的鹼基進行置換，鹼基（無鹼基核苷酸）或綴合鹼基的去除，(c)糖修飾（例如，在2'位置或4'位置處）或糖的置換，以及(d)主鏈修飾，包括磷酸二酯鍵的修飾或置換。可用於本發明的INHBE dsRNA藥劑、INHBE反義多核苷酸和INHBE有義多核苷酸的某些實施方案中的RNA化合物的具體示例，包括但不限於包含經修飾的主鏈或沒有天然核苷間鍵的RNA。作為非限制性示例，具有經修飾的主鏈的RNA可在該主鏈中不具有磷原子。在其核苷間主鏈中不具有磷原子的RNA可被稱為寡核苷。在本發明的某些實施方案中，經修飾的RNA在其核苷間主鏈中具有磷原子。

【0136】 應當理解，術語“RNA分子”或“RNA”或“核糖核酸分子”不僅涵蓋如在自然界中表達或發現的RNA分子，而且還涵蓋如本文所述或如本領域已知的包含一種或多種核糖核苷酸/核糖核苷類似物或衍生物的RNA類似物和衍生物。術語“核糖核苷”和“核糖核苷酸”在本文中可互換使用。RNA分子可在核鹼基結構或核糖-磷酸酯主鏈結構中進行修飾，例如，如本文下文所述，並且包含核糖核苷類似物或衍生物的分子必須保留形成雙鏈體的能力。作為非限制性示例，RNA分子還可包含至少一個經修飾的核糖核苷，包括但不限於經2'-O-甲基修飾的核苷、包含5'硫代磷酸酯基團的核苷、與膽甾醇基衍生物或十二烷酸雙癸醯胺基團連接的末端核苷、鎖核苷、無鹼基核苷、經2'-脫氧-2'-氟修飾的核苷、經2'-氨基修飾的核苷、經2'-烷基修飾的核苷、嗎啉基核苷、包含氨基磷酸酯或非天然鹼基的核苷或它們的任何組合。在本發明的一些實施方案中，RNA分子包含至少1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20

個或至多全長的INHBE dsRNA藥劑分子的核糖核苷，其為經修飾的核糖核苷。對於RNA分子中的此類多個經修飾的核糖核苷中的每一者，修飾不必是相同的。

【0137】 在一些實施方案中，本發明的DsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸可包含一個或多個獨立選擇的經修飾的核苷酸和/或一個或多個獨立選擇的非磷酸二酯鍵。如本文所用，術語“獨立選擇”用於指所選的元件，諸如經修飾的核苷酸、非磷酸二酯鍵等，意指兩個或更多個所選的元件可以但不必彼此相同。

【0138】 如本文所用，“核苷酸鹼基”、“核苷酸”或“核鹼基”是雜環嘧啶或嘌呤化合物，是所有核酸的標準組成部分，並且包括形成核苷酸腺嘌呤、鳥嘌呤、胞嘧啶、胸腺嘧啶和尿嘧啶的鹼基。核鹼基可進一步被修飾以包括（儘管並非旨在進行限制）：通用鹼基、疏水性鹼基、混雜鹼基、尺寸擴大的鹼基和氟化鹼基。術語“核糖核苷酸”或“核苷酸”可在本文中用於指未修飾的核苷酸、經修飾的核苷酸或替代置換部分。本領域技術人員將認識到鳥嘌呤、胞嘧啶、腺嘌呤和尿嘧啶可被其他部分置換，而基本上不改變包含帶有此類置換部分的核苷酸的寡核苷酸的鹼基配對特性。

【0139】 在一個實施方案中，考慮了用於本文所述的方法和組合物的經修飾的RNA是肽核酸（PNA），其具有形成期望的雙鏈體結構的能力並且允許或介導經由RISC途徑特異性降解靶RNA。在本發明的某些實施方案中，INHBE RNA干擾劑包含與靶INHBE RNA序列相互作用以指導靶INHBE RNA的切割的單鏈RNA。

【0140】 經修飾的RNA主鏈可包括，例如，硫代磷酸酯、手性硫代磷

酸酯、二硫代磷酸酯、磷酸三酯、氨基烷基磷酸三酯、甲基和其他烷基膦酸酯（包括3'-亞烷基膦酸酯和手性膦酸酯）、亞膦酸酯、氨基磷酸酯（包括3'-氨基磷酸酯和氨基烷基氨基磷酸酯）、硫代氨基磷酸酯、硫代烷基膦酸酯、硫代烷基磷酸三酯和具有正常3'-5'鍵的硼代磷酸酯、這些硼代磷酸酯的2'-5'連接的類似物，以及那些具有相反極性的化合物，其中相鄰的核苷單元對是3'-5'連接至5'-3'或者2'-5'連接至5'-2'。還包括各種鹽、混合鹽和游離酸形式。製備含磷鍵的方式是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑、某些經修飾的INHBE反義多核苷酸和/或某些經修飾的INHBE有義多核苷酸。

【0141】 其中不包含磷原子的經修飾的RNA主鏈具有由短鏈烷基或環烷基核苷間鍵、混合雜原子和烷基或環烷基核苷間鍵、或一個或多個短鏈雜原子或雜環核苷間鍵形成的主鏈。這些主鏈包括具有嗎啉鍵（部分地由核苷的糖部分形成）的那些主鏈；矽氧烷主鏈；硫化物、亞碸和碸主鏈；甲醯基和硫代甲醯基主鏈；亞甲基甲醯基和硫代甲醯基主鏈；含烯烴的主鏈；氨基磺酸鹽主鏈；亞甲基亞氨基和亞甲基肼基主鏈；磺酸鹽和磺醯胺主鏈；醯胺主鏈；以及其他具有混合的N、O、S和CH_2組成部分的主鏈。製備不包含磷原子的經修飾的RNA主鏈的方式是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑、某些經修飾的INHBE反義多核苷酸和/或某些經修飾的INHBE有義多核苷酸。

【0142】 在本發明的某些實施方案中，RNA模擬物被包含在INHBE dsRNA、INHBE反義多核苷酸和/或INHBE有義多核苷酸中，諸如但不限於：用新的基團置換核苷酸單元的糖和核苷間鍵，即主鏈。在此類實施方

案中，保持鹼基單位用於與合適的INHBE核酸靶標化合物雜交。一種這樣的寡聚化合物，已被證明具有優異雜交特性的RNA模擬物，被稱為肽核酸（PNA）。在PNA化合物中，RNA的糖主鏈被含有醯胺的主鏈，特別是氨基乙基甘氨酸主鏈置換。核鹼基被保留並直接或間接地結合到主鏈的醯胺部分的氮雜氮原子。製備RNA模擬物的方式是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑。

【0143】 本發明的一些實施方案包括具有硫代磷酸酯主鏈的RNA和具有雜原子主鏈的寡核苷，並且特別是-CH_2-NH-CH_2-、-CH_2-N(CH_3)-O-CH_2-[已知為亞甲基(甲基亞氨基)或MMI主鏈]、-CH_2-O-N(CH_3)-CH_2-、-CH_2-N(CH_3)-N(CH_3)-CH_2-和-N(CH_3)-CH_2-[其中天然磷酸二酯主鏈被表示為-O-P-O-CH_2-]。製備具有硫代磷酸酯主鏈的RNA和具有雜原子主鏈的寡核苷的方式是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑、某些INHBE反義多核苷酸和/或某些INHBE有義多核苷酸。

【0144】 經修飾的RNA還可包含一個或多個經取代的糖部分。本發明的INHBE dsRNA、INHBE反義多核苷酸和/或INHBE有義多核苷酸可在2'位置處包含以下項中的一者：OH；F；O-、S-或N-烷基；O-、S-或N-烯基；O-、S-或N-炔基；或O-烷基-O-烷基，其中該烷基、烯基和炔基可以是經取代或未取代的C_1至C_{10}烷基或C_2至C_{10}烯基和炔基。示例性的合適修飾包括O[$(CH_2)_nO]_mCH_3$、$O(CH_2)_nOCH_3$、$O(CH_2)_nNH_2$、$O(CH_2)_nCH_3$、$O(CH_2)_nONH_2$和$O(CH_2)_nON[(CH_2)_nCH_3)]_2$，其中n和m為1至約10。在其他實施方案中，dsRNA在2'位置處包含以下項中的一者：C_1至C_{10}低級烷基、

經取代的低級烷基、烷芳基、芳烷基、O-烷芳基或O-芳烷基、SH、SCH_3、OCN、Cl、Br、CN、CF_3、OCF_3、$SOCH_3$、SO_2CH_3、ONO_2、NO_2、N_3、NH_2、雜環烷基、雜環烷芳基、氨基烷基氨基、聚烷基氨基、經取代的甲矽烷基、RNA切割基團、報告基團、嵌入劑、用於改善INHBE dsRNA藥劑的藥代動力學特性的基團，或用於改善INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的藥效學特性的基團，以及具有類似特性的其他取代基。在一些實施方案中，修飾包括2'-甲氧基乙氧基（2'-O-$CH_2CH_2OCH_3$，也稱為2'-O-(2-甲氧基乙基)或2'-MOE）（Martin等人，Helv.Chim.Acta, 1995, 78:486-504），即烷氧基-烷氧基基團。另一個示例性的修飾是2'-二甲基氨基氧基乙氧基，即$O(CH_2)_2ON(CH_3)_2$基團（也稱為2'-DMAOE，如本文下文的示例所述），和2'-二甲基氨基乙氧基乙氧基（本領域也稱為2'-O-二甲基氨基乙氧基乙基或2'-DMAEOE），即2'-O-CH_2-O-CH_2-$N(CH_2)_2$。製備經修飾的RNA的方式（諸如那些描述的方式）是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑。

【0145】 其他修飾包括2'-甲氧基（2'-OCH_3）、2'-氨基丙氧基（2'-$OCH_2CH_2CH_2NH_2$）和2'-氟（2'-F）。類似的修飾還可在本發明的INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的RNA上的其他位置處進行，特別是在3'末端核苷酸上或在2'-5'連接的INHBE dsRNA、INHBE反義多核苷酸或INHBE有義多核苷酸中的糖的3'位置，以及5'末端核苷酸的5'位置。INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸還可具有糖模擬物，諸如用環丁基部分代替呋喃戊糖

基糖。製備經修飾的RNA的方式（諸如那些描述的方式）是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸。

【0146】 在一些實施方案中，INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸可包含核鹼基（在本領域中經常簡稱為“鹼基”）修飾或取代。如本文所用，“未修飾的”或“天然的”核鹼基包括嘌呤鹼基腺嘌呤和鳥嘌呤，以及嘧啶鹼基胸腺嘧啶、胞嘧啶和尿嘧啶。經修飾的核鹼基包括其他合成的核鹼基和天然的核鹼基，諸如5-甲基胞嘧啶（5-Me-C），5-羥甲基胞嘧啶，黃嘌呤，次黃嘌呤，2-氨基腺嘌呤，腺嘌呤和鳥嘌呤的6-甲基和其他烷基衍生物，腺嘌呤和鳥嘌呤的2-丙基和其他烷基衍生物，2-硫代尿嘧啶，2-硫代胸腺嘧啶和2-硫代胞嘧啶，5-鹵代尿嘧啶和胞嘧啶，5-丙炔基尿嘧啶和胞嘧啶，6-偶氮尿嘧啶、胞嘧啶和胸腺嘧啶，5-尿嘧啶（假尿嘧啶），4-硫代尿嘧啶，8-鹵代、8-氨基、8-硫醇、8-硫代烷基、8-羥基和其他8-取代的腺嘌呤和鳥嘌呤，5-鹵代（特別是5-溴代）、5-三氟甲基和其他5-取代的尿嘧啶和胞嘧啶，7-甲基鳥嘌呤和7-甲基腺嘌呤，8-氮雜鳥嘌呤和8-氮雜腺嘌呤，7-脫氮鳥嘌呤和7-脫氮腺嘌呤，以及3-脫氮鳥嘌呤和3-脫氮腺嘌呤。可包含在本發明的INHBE dsRNA藥劑的某些實施方案中的其他核鹼基是本領域已知的，參見例如：“生物化學、生物技術和醫學中的經修飾的核苷（Modified Nucleosides in Biochemistry, Biotechnology and Medicine）”，Herdewijn, P.編輯，Wiley-VCH, 2008；“聚合物科學與工程的簡明百科全書（The Concise Encyclopedia Of Polymer Science And Engineering）”，第858-859頁，Kroschwitz, J. L編輯，John Wiley & Sons,

1990；English等人，“應用化學，國際版（Angewandte Chemie, International Edition）”，1991, 30, 613；Sanghvi, Y S.，“dsRNA研究與應用（dsRNA Research and Applications）”，第15章第289-302頁，Crooke, S. T.和Lebleu, B.編輯，CRC Press, 1993。製備包含核鹼基修飾和/或取代（諸如本文所述的那些）的dsRNA、INHBE反義鏈多核苷酸和/或INHBE有義鏈多核苷酸的方式是本領域常規實踐的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑、INHBE有義多核苷酸和/或INHBE反義多核苷酸。

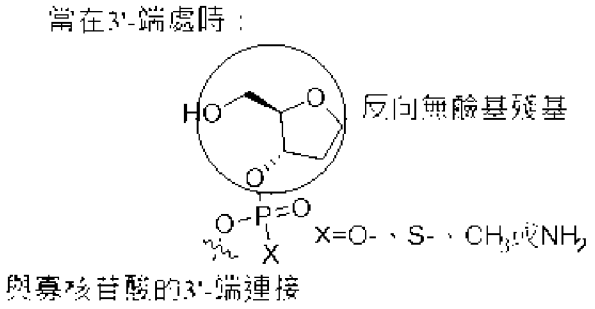
【0147】 本發明的INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的某些實施方案包括經修飾以包含一個或多個鎖核酸（LNA）的RNA。鎖核酸是具有經修飾的核糖部分的核苷酸，該經修飾的核糖部分包含連接2'碳和4'碳的額外的橋。該結構有效地將核糖“鎖定”在3'-內結構構象中。在本發明的INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸中添加鎖核酸可增加血清的穩定性，並降低脫靶效應（Elmen, J.等人，(2005) Nucleic Acids Research 33(1):439-447；Mook, O R.等人，(2007)Mol Canc Ther 6(3):833-843；Grunweller, A.等人，(2003) Nucleic Acids Research 31(12):3185-3193）。製備包含鎖核酸的dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的方式是本領域常規實施的，並且此類方法可用於製備本發明的某些經修飾的INHBE dsRNA藥劑。

【0148】 本發明的INHBE dsRNA化合物、有義多核苷酸和/或反義多核苷酸的某些實施方案包含至少一個經修飾的核苷酸，其中該至少一個經

修飾的核苷酸包括：2'-O-甲基核苷酸、2'-氟核苷酸、2'-脫氧核苷酸、2'3'-開環核苷酸模擬物、鎖核苷酸、2'-F-阿拉伯糖核苷酸、2'-甲氧基乙基核苷酸、經2'-氨基修飾的核苷酸、經2'-烷基修飾的核苷酸、嗎啉基核苷酸和3'-OMe核苷酸，包含5'-硫代磷酸酯基團的核苷酸、包含乙烯基膦酸酯的核苷酸、包含腺苷-乙二醇核酸（GNA）的核苷酸、包含胸苷-乙二醇核酸（GNA）S-異構體的核苷酸、包含2'-脫氧胸苷-3'磷酸酯的核苷酸、包含2'-脫氧鳥苷-3'-磷酸酯的核苷酸、包含2'-脫氧腺苷-3'-磷酸酯的核苷酸、包含2'-脫氧胞苷-3'-磷酸酯的核苷酸、包含2'-脫氧尿苷-3'-磷酸酯的核苷酸、或與膽甾醇基衍生物或十二烷酸雙癸醯胺基團連接的末端核苷酸、經2'-氨基修飾的核苷酸、包含氨基磷酸酯或非天然鹼基的核苷酸。在一些實施方案中，INHBE dsRNA化合物包含在反義鏈（在本文也稱為引導鏈）的5′-端處的E-乙烯基膦酸酯核苷酸。

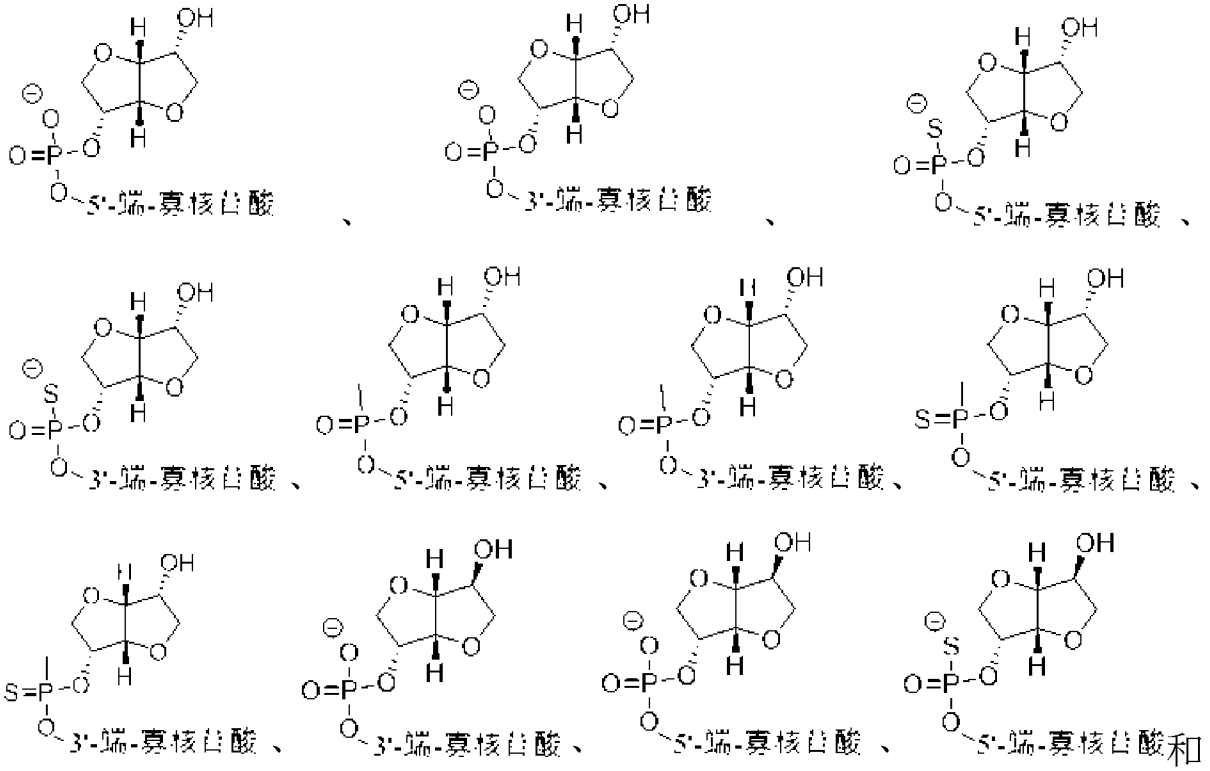
【0149】 本發明的INHBE dsRNA化合物、有義多核苷酸的3'端和5'端和/或反義多核苷酸的3'端的某些實施方案包含至少一個經修飾的核苷酸，其中該至少一個經修飾的核苷酸包括：無鹼基核苷酸、核糖醇、反向核苷酸、反向無鹼基核苷酸、反向2'-OMe核苷酸、反向2'-脫氧核苷酸。本領域技術人員已知的是，在寡核苷酸的末端處包含無鹼基核苷酸或反向無鹼基核苷酸增強了穩定性（Czauderna等人，“哺乳動物細胞中合成siRNA的結構變異和穩定修飾（Structural variations and stabilizing modifications of synthetic siRNAs in mammalian cells.）”，Nucleic Acids Res.2003;31(11):2705-2716. doi:10.1093/nar/gkg393）。在一些實施方案中，INHBE dsRNA化合物在3'-端或5'-端處或者3'-端和5'-端兩者處包含一

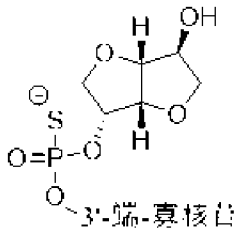
個或多個反向無鹼基殘基（invab）。示例性的反向無鹼基殘基（invab）包括但不限於以下項：



。

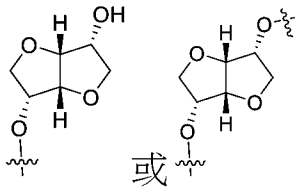
【0150】 本發明的INHBE dsRNA化合物、有義多核苷酸的3'端和5'端和/或反義多核苷酸的3'端的某些實施方案包含至少一個經修飾的核苷酸，其中該至少一個經修飾的核苷酸包括：異甘露醇核苷酸或所述異甘露醇核苷酸的立體異構體。異甘露醇核苷酸或所述異甘露醇核苷酸的立體異構體的具體示例包括但不限於：





3'-端-寡核苷酸，其中短語“寡核苷酸”各自獨立地表示多核苷酸部分。

示例性的異甘露醇殘基（imann）包括但不限於以下項：



或 。

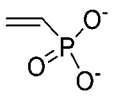
【0151】 在某些實施方案中，這些異甘露醇核苷酸可與一個或多個靶向基團或遞送分子（諸如GalNAc部分）進一步綴合。

【0152】 本發明的INHBE dsRNA化合物、反義多核苷酸的某些實施方案包含至少一個經修飾的核苷酸，其中該至少一個經修飾的核苷酸包括非鎖核酸核苷酸（UNA）或/和乙二醇核酸核苷酸（GNA）。本領域技術人員已知的是，UNA和GNA是能夠顯著改善siRNA化合物的脫靶分佈的熱不穩定的化學修飾（Janas等人，“對具有有限脫靶驅動的大鼠肝毒性的GalNAc-綴合的siRNA選擇（Selection of GalNAc-conjugated siRNAs with limited off-target-driven rat hepatotoxicity.）”，Nat Commun.2018;9(1):723. doi:10.1038/s41467-018-02989-4；Laursen等人，“利用非鎖核酸（UNA）來增強siRNA在體外和體內的性能（Utilization of unlocked nucleic acid (UNA) to enhance siRNA performance in vitro and in vivo.）”，Mol BioSyst.2010;6:862–70）。

【0153】 本發明的INHBE dsRNA化合物、反義多核苷酸的某些實施方案還包含5'-磷酸酯模擬物。在某些實施方案中，5'-磷酸酯模擬物在RNAi

藥劑的反義鏈上。如本文所用，“5'-磷酸酯模擬物”或“膦酸酯模擬物”是指對應於與核苷酸（例如，核糖或脫氧核糖或其類似物）的糖部分（或在糖替代置換部分的相當位置處）的5'-碳結合的磷酸酯類似物部分。通常，該磷酸酯類似物是乙烯基膦酸酯，其中該乙烯基膦酸酯基團的碳原子與糖部分或其類似物的4'-碳結合。在其他實施方案中，該磷酸酯類似物是乙基膦酸酯、環狀膦酸酯、氧基甲基膦酸酯、硫代甲基膦酸酯或氨基甲基膦酸酯，其中該硫代甲基基團的碳、氧、硫或胺原子或該氨基甲基基團的氮原子與糖部分或其類似物的4'-碳結合。在此類情況下，期望的是穩定的磷模擬物，防止可能使該化合物失活的降解或去磷酸化。因此，在某些實施方案中，其中5'-磷模擬物已被穩定的寡核苷酸是期望的。在某些此類實施方案中，與未修飾的核苷相比，磷模擬物在生物系統中不易被去除，並且/或5'-核苷不易被核酸酶切割。合適的磷酸鹽模擬物公開於例如WO2011005860、WO2011/139702、WO2013/033230、WO2010/048585、WO2010/048549、WO2011/139699、WO2017214112、WO2018045317中，這些文獻中的每一篇的內容以引用方式併入本文以用於本文提供的方法。

【0154】 在一些實施方案中，該磷酸酯模擬物是5'-乙烯基膦酸酯（VP）。在示例性的實施方案中，本公開內容的乙烯基膦酸酯具有以下結構：

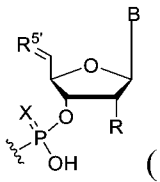


。

【0155】 本公開內容的乙烯基膦酸酯可與本公開內容的dsRNA的反義鏈或有義鏈連接。在某些優選的實施方案中，本公開內容的乙烯基膦酸

酯與dsRNA的反義鏈連接，任選地位於該dsRNA的反義鏈的5'端處。

【0156】 在某些實施方案中，本公開內容的經乙烯基膦酸酯修飾的核苷酸具有式(IV)的結構：



(IV)；

其中X為O或S；

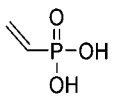
R為氫、羥基、氟或C_{1-20}烷氧基（例如，甲氧基或正十六烷氧基）；

$R^{5'}$為=C(H)-P(O)$(OH)_2$，並且C5'碳和R5'之間的雙鍵處於E或Z取向（例如，E取向）；並且

B為核鹼基或經修飾的核鹼基，任選地其中B為腺嘌呤、鳥嘌呤、胞嘧啶、胸腺嘧啶或尿嘧啶。

【0157】 在某些實施方案中，$R^{5'}$為=C(H)-P(O)$(OH)_2$，並且C5'碳和R5'之間的雙鍵處於E取向。在某些實施方案中，R為甲氧基，$R^{5'}$為=C(H)-P(O)$(OH)_2$，並且C5'碳和R5'之間的雙鍵處於E取向。在某些實施方案中，X為S，R為甲氧基，R5'為=C(H)-P(O)$(OH)_2$，並且C5'碳和R5'之間的雙鍵處於E取向。

【0158】 對於本公開內容的dsRNA、組合物和方法，還考慮了乙烯基膦酸酯修飾。示例性的乙烯基膦酸酯結構是：



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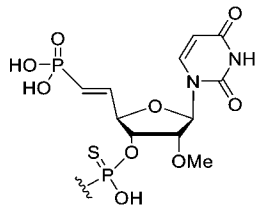
【0159】 在某些實施方案中，經乙烯基膦酸酯修飾的核苷酸是具有如下結構的VPu*：



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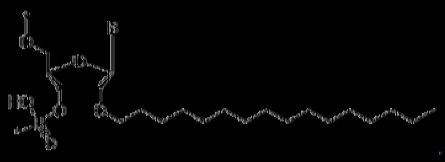
【0160】 在許多情況下，保護基團在本發明化合物的製備期間使用。如本文所用，術語“受保護的”意指所指定的部分具有添加在其上的保護基團。在本發明的一些實施方案中，化合物含有一個或多個保護基團。在本發明的方法中可採用各種保護基團。一般來講，保護基團使得化學官能團對特定反應條件呈惰性，並且可在分子中添加或去除此類官能團上而基本上不破壞該分子的其餘部分。一般來講，保護基團（特別是羥基保護基團）是本領域熟知的（Greene和Wuts，“有機合成中的保護基團（Protective Groups in Organic Synthesis）”，第2章，第2版，John Wiley & Sons, New York, 1991）。

【0161】 如本文所用，保護基團（例如，羥基保護基團）的示例包括但不限於甲基、乙基、苄基（Bn）、苯基、異丙基、叔丁基、乙醯基、氯乙醯基、三氯乙醯基、新戊醯基、叔丁氧基甲基、甲氧基甲基、1-乙氧基乙基、1-(2-氯乙氧基)乙基、烯丙基、環己基、9-芴基甲氧基羰基（Fmoc）、甲磺酸酯、甲苯磺酸酯、三氟甲磺酸酯、苯甲醯基、苯甲醯基甲酸酯、對苯基苯甲醯基、4-甲氧基苄基、單甲氧基三苯甲基、二甲氧基三苯甲基、三甲氧基三苯甲基、4-氯苄基、4-硝基苄基、2,4-二硝基苯基、4-醯氧基苄基、2-甲基苯基、2,6-二甲基苯基、2-氯苯基、2,6-二氯苄基、二苯基甲基、三苯基甲基、4-甲硫基-1-丁基、S-乙醯基硫代乙酸酯（SATA）、2-氰基乙基、2-氰基、1-二甲基乙基（CDM）、4-氰基-2-丁烯基、2-(三甲基甲矽烷基)

乙基（TSE）、2-(苯硫基)乙基、2-(三苯基甲矽烷基)乙基、2-(苄基磺醯基)乙基、2,2,2-三氯乙基、2,2,2-三溴乙基、2,3-二溴丙基、2,2,2-三氟乙基、苯硫基、2-氯-4-三苯甲基苯基、2-溴苯基、2-[N-異丙基-N-(4-甲氧基苯甲醯基)氨基]乙基、4-(N-三氟乙醯基氨基)丁基、4-氧代戊基、4-三苯甲基氨基苯基、4-苄基氨基苯基、四氫吡喃基、嗎啉基、三甲基甲矽烷基、三乙基甲矽烷基、叔丁基二甲基甲矽烷基、叔丁基二苯基甲矽烷基、三苯基甲矽烷基、三異丙基甲矽烷基、新戊醯基氧基甲基（POM）和9-苯基黃嘌呤-9-基。

【0162】 如本文所用，氨基保護基團的示例包括但不限於氨基甲酸保護基團，諸如2-三甲基甲矽烷基乙氧基羰基（Teoc）、1-甲基-1-(4-聯苯)乙氧基羰基（Bpoc）、叔丁氧基羰基（BOC）、烯丙基氧基羰基（Alloc）、9-芴基-甲氧基羰基（Fmoc）、苄氧基羰基（Cbz）；醯胺保護基團，諸如甲醯基、乙醯基、新戊醯基、三鹵代乙醯基、苯甲醯基、2-硝基苯磺醯基；以及亞胺和環狀醯亞胺保護基團，諸如鄰苯二甲醯亞胺基和二硫代琥珀醯基。這些氨基保護基團的等同物也被涵蓋在本發明的化合物和方法中。

【0163】 INHBE dsRNA化合物的某些實施方案包含至少一個親脂性部分，例如但不限於其中含有飽和或不飽和的C_{16}烴鏈（例如，線性C16烷基或烯基）的親脂性部分。親脂性部分被包含在本申請所提供的任何位置中。在一些實施方案中，親脂性部分與雙鏈iRNA藥劑的核鹼基、糖部分或核苷間鍵綴合。例如，C_{16}部分可經由如以下結構所示的核糖核苷酸的2'-氧進行綴合：



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〔0164〕 如本文所用，“親油基”或“親脂性部分”廣義地指對脂質具有親和力的任何化合物或化學部分。表徵親脂性部分的親脂性的一種方法是通過辛醇-水分配係數logKow，其中Kow是在兩相體系處於平衡時化學物質在辛醇相中的濃度與其在水相中的濃度的比率。辛醇-水分配係數是物質的實驗室測量屬性。然而，也可通過使用與化學物質的結構組成有關的係數來預測，這些係數是使用第一原理或經驗性方法計算的(參見例如，Tetko等人，J. Chem.Inf.Comput.Sci.41:1407-21 (2001))，該文獻以引用方式全文併入本文。它提供了物質傾向於優選非水性或油性環境而不是水的熱力學量度（即，其親水性/親脂性平衡）。原則上，當化學物質的logKow超過0時，該化學物質具有親脂性。

〔0165〕 可包含在本發明的INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的某些實施方案的RNA中的另一種修飾包括將一個或多個配體、部分或綴合物以化學方式連接至RNA，這些配體、部分或綴合物分別增強INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的一種或多種特徵。可被增強的特徵的非限制性示例是：INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸活性，細胞分佈，INHBE dsRNA藥劑的遞送，INHBE dsRNA藥劑的藥代動力學特性，以及INHBE dsRNA藥劑的細胞攝取。在本發明的一些實施方案中，INHBE dsRNA藥劑包含一個或多個在本發明的INHBE dsRNA藥劑的某些實施方案中與有義鏈綴合的靶向基團或連接基團。靶向基團的非限

制性示例是包含N-乙醯基-半乳糖胺(GalNAc)的化合物。術語“靶向基團”、“靶向劑”、“連接劑”、“靶向化合物”、“遞送分子”、“遞送化合物”和“靶向配體”在本文中可互換使用。在本發明的某些實施方案中，INHBE dsRNA藥劑包含與有義鏈的5'-末端綴合的靶向化合物。在本發明的某些實施方案中，INHBE dsRNA藥劑包含與有義鏈的3'-末端綴合的靶向化合物。在本發明的一些實施方案中，INHBE dsRNA藥劑包含含有GalNAc的靶向基團。在本發明的某些實施方案中，INHBE dsRNA藥劑不包含與有義鏈的3'-末端和5'-末端中的一者或兩者綴合的靶向化合物。在本發明的某些實施方案中，INHBE dsRNA藥劑不包含與有義鏈的5'-末端和3'-末端中的一者或兩者綴合的含GalNAc的靶向化合物。

【0166】 附加靶向劑和連接劑是本領域熟知的，例如，可用於本發明的某些實施方案的靶向劑和連接劑包括但不限於脂質部分，諸如膽固醇部分（Letsinger等人，Proc.Natl.Acid.Sci.USA, 1989, 86: 6553-6556）；膽酸（Manoharan等人，Biorg.Med.Chem.Let., 1994, 4:1053-1060）；硫醚，例如綠柱石-S-三苯甲基硫醇（Manoharan等人，Ann.N.Y.Acad.Sci., 1992, 660:306-309；Manoharan等人，Biorg.Med.Chem.Let., 1993, 3:2765-2770）；硫代膽固醇（Oberhauser等人，Nucl.Acids Res., 1992, 20:533-538）；脂族鏈，例如十二烷二醇或十一烷基殘基（Saison-Behmoaras等人，EMBO J, 1991, 10:1111-1118；Kabanov等人，FEBS Lett., 1990, 259:327-330；Svinarchuk等人，Biochimie, 1993, 75:49-54）；磷脂，例如二-十六烷基-外消旋-甘油或三乙基-銨1,2-二-O-十六烷基-外消旋-甘油-3-膦酸酯（Manoharan等人，Tetrahedron Lett., 1995, 36:3651-3654；Shea等人，

Nucl.Acids Res., 1990, 18:3777-3783）；聚胺或聚乙二醇鏈（Manoharan等人，Nucleosides & Nucleotides, 1995, 14:969-973）；或金剛烷乙酸（Manoharan等人，Tetrahedron Lett., 1995, 36:3651-3654）；棕櫚醯基部分（Mishra等人，Biochim.Biophys.Acta, 1995, 1264:229-237）；或十八胺或己基氨基-羰基氧基膽固醇部分（Crooke等人，J. Pharmacol.Exp.Ther., 1996, 277:923-937）。

【0167】包含INHBE dsRNA藥劑、INHBE反義多核苷酸和/或INHBE有義多核苷酸的組合物的某些實施方案可包含改變INHBE dsRNA藥劑的分佈、靶向等的配體。在包含本發明的INHBE dsRNA藥劑的組合物的一些實施方案中，例如與缺乏此類配體的物種相比，該配體增加了對所選的靶標的親和力，所選的靶標例如分子、細胞或細胞類型、區室，例如細胞或器官區室、組織、器官或身體區域。可用於本發明的組合物和/或方法的配體可以是天然存在的物質，諸如蛋白質（例如人血清白蛋白（HSA）、低密度脂蛋白（LDL）或球蛋白）；碳水化合物（例如葡聚糖、普魯蘭多糖、幾丁質、脫乙醯殼多糖、菊粉、環糊精或透明質酸）；或脂質。配體也可以是重組分子或合成分子，諸如合成聚合物，例如合成聚氨基酸或聚胺。聚氨基酸的示例是聚賴氨酸（PLL）、聚L-天冬氨酸、聚L-谷氨酸、苯乙烯-馬來酸酐共聚物、聚(L-丙交酯-共-乙醇酸)共聚物、二乙烯基醚-馬來酸酐共聚物、N-(2-羥丙基)甲基丙烯醯胺共聚物（HMPA）、聚乙二醇（PEG）、聚乙烯醇（PVA）、聚氨酯、聚(2-乙基丙烯酸)、N-異丙基丙烯醯胺聚合物或聚膦嗪。聚胺的示例包括：聚乙烯亞胺、聚賴氨酸（PLL）、精胺、亞精胺、聚胺、偽肽-聚胺、肽模擬物聚胺、樹枝狀聚胺、精氨酸、脒、魚精蛋

白、陽離子脂質、陽離子卟啉、聚胺的季鹽、或α螺旋肽。

【0168】包含在本發明的組合物和/或方法中的配體可包括靶向基團，其非限制性示例是細胞或組織靶向劑，例如凝集素、糖蛋白、脂質或蛋白質，例如與特定細胞類型諸如腎臟細胞或肝臟細胞結合的抗體。靶向基團可以是促甲狀腺素、促黑素、凝集素、糖蛋白、表面活性劑蛋白A、黏蛋白碳水化合物、多價乳糖、多價半乳糖、N-乙醯基-半乳糖胺、N-乙醯基-古洛糖胺多價甘露糖、多價岩藻糖、糖基化聚氨基酸、多價半乳糖、轉鐵蛋白、雙膦酸鹽、聚谷氨酸鹽、聚天冬氨酸鹽、脂質、膽固醇、類固醇、膽汁酸、葉酸鹽、維生素B12、維生素A、生物素或RGD肽或RGD肽模擬物。

【0169】配體的其他示例包括染料、嵌入劑（例如吖啶）、交聯劑（例如補骨脂素、絲裂黴素C）、卟啉（TPPC4、德克薩斯卟啉（texaphyrin）、噻啉（sapphyrin））、多環芳烴（例如吩嗪、二氫吩嗪）、人工核酸內切酶（例如EDTA）、親脂性分子（例如膽固醇、膽酸、金剛烷乙酸、1-芘丁酸、二氫睾酮、1,3-雙-O(十六烷基)甘油、香葉氧基己基基團、十六烷基甘油、冰片、薄荷醇、1,3-丙二醇、十七烷基基團、棕櫚酸、肉豆蔻酸、O3-(油醯基)石膽酸、O3-(油醯基)膽烯酸、二甲氧基三苯甲基或吩噁嗪）和肽綴合物（例如觸足肽、Tat肽）、烷化劑、磷酸酯、氨基、巰基、PEG（例如PEG-40K）、MPEG、$[MPEG]_2$、聚氨基、烷基、經取代的烷基、放射性標記物、酶、半抗原（例如，生物素）、轉運/吸收促進劑（例如，阿司匹林、維生素E、葉酸）、合成核糖核酸酶（例如，咪唑、雙咪唑、組胺、咪唑簇、吖啶-咪唑綴合物、四氮雜大環的Eu3+複合物）、二硝基苯基、HRP或AP。

【0170】包含在本發明的組合物和/或方法中的配體可以是蛋白質（例如糖蛋白或肽，例如對共配體具有特定親和力的分子），或抗體，例如與特定細胞類型諸如癌細胞、內皮細胞、心臟細胞或骨細胞結合的抗體。可用於本發明的組合物和/或方法的實施方案中的配體可以是激素或激素受體。可用於本發明的組合物和/或方法的實施方案中的配體可以是脂質、凝集素、碳水化合物、維生素、輔因子、多價乳糖、多價半乳糖、N-乙醯基-半乳糖胺、N-乙醯基-古洛糖胺多價甘露糖、或多價岩藻糖。可用於本發明的組合物和/或方法的實施方案中的配體可以是能夠促進細胞攝取INHBE dsRNA藥劑的物質，例如通過破壞細胞的細胞骨架，例如通過破壞細胞的微管、微絲和/或中間絲。這種類型的藥劑的非限制性示例是：taxon、長春新鹼、長春花鹼、細胞鬆弛素、諾考達唑、促進微絲聚合劑（japlakinolide）、微絲解聚素A、鬼筆環肽、微絲細胞骨架解聚劑（swinholide）A、印丹諾辛（indanocine）和myoservin。

【0171】在一些實施方案中，與本發明的INHBE dsRNA藥劑連接的配體作為藥代動力學（PK）調節劑起作用。可用於本發明的組合物和方法中的PK調節劑的一個示例包括但不限於：親油基、膽汁酸、類固醇、磷脂類似物、肽、蛋白質結合劑、PEG、維生素、膽固醇、脂肪酸、膽酸、石膽酸、二烷基甘油酯、二醯基甘油酯、磷脂、鞘脂、萘普生、布洛芬、維生素E、生物素、結合血清蛋白的適體等。還已知包含多個硫代磷酸酯鍵的寡核苷酸與血清蛋白結合，因此主鏈中包含多個硫代磷酸酯鍵的短寡核苷酸（例如具有約5個鹼基、10個鹼基、15個鹼基或20個鹼基的寡核苷酸）也可在本發明的組合物和/或方法中用作配體。

INHBE dsRNA藥劑組合物

【0172】 在本發明的一些實施方案中，INHBE dsRNA藥劑存在於組合物中。本發明的組合物可包含一種或多種INHBE dsRNA藥劑和以下項中任選的一者或多者：藥學上可接受的載劑、遞送劑、靶向劑、可檢測標記等。根據本發明的方法的一些實施方案可使用的靶向劑的非限制性示例是將本發明的INHBE dsRNA藥劑引導至待治療的細胞和/或進入待治療的細胞中的藥劑。對靶向劑的選擇將取決於以下因素：INHBE相關疾病或病症的性質，以及所靶向的細胞類型。在一個非限制性示例中，在本發明的一些實施方案中，可能期望將INHBE dsRNA藥劑靶向肝臟細胞和/或進入該肝臟細胞中。應當理解，在本發明的方法的一些實施方案中，治療劑包括僅具有遞送劑的INHBE dsRNA藥劑，諸如包含N-乙醯半乳糖胺（GalNAc）的遞送劑，而沒有任何附加連接元件。例如，在本發明的一些方面，INHBE dsRNA藥劑可與包含GalNAc的遞送化合物連接並被包含在含有藥學上可接受的載劑的組合物中，並且在沒有任何與INHBE dsRNA藥劑連接的可檢測標記或靶向劑等的情況下施用於細胞或受試者。

【0173】 在本發明的INHBE dsRNA藥劑與一種或多種遞送劑、靶向劑、標記劑等一起施用和/或與該一種或多種遞送劑、靶向劑、標記劑等連接的情況下，技術人員將知道並且能夠選擇和使用用於本發明的方法的合適藥劑。標記劑可在本發明的某些方法中用於測定INHBE dsRNA藥劑在細胞和組織中的位置，並且可用於測定已經在本發明的方法中施用的包含INHBE dsRNA藥劑的治療組合物在細胞、組織或器官中的位置。用於連接

和利用標記劑諸如酶標記、染料、放射性標記等的方法是本領域熟知的。應當理解，在本發明的組合物和方法的一些實施方案中，標記劑與包含在INHBE dsRNA藥劑中的有義多核苷酸和反義多核苷酸中的一者或兩者連接。

INHBE dsRNA藥劑和INHBE反義多核苷酸藥劑的遞送

【0174】 本發明的方法的某些實施方案包括將INHBE dsRNA藥劑遞送至細胞中。如本文所用，術語“遞送”意指促進或實現細胞攝取或吸收。INHBE dsRNA藥劑的吸收或攝取可通過無輔助的擴散或主動細胞過程發生，或者通過使用可與本發明的INHBE dsRNA藥劑締合的遞送劑、靶向劑等發生。適用於本發明的方法的遞送方式包括但不限於：體內遞送，其中將INHBE dsRNA藥劑注射到組織部位或全身性施用。在本發明的一些實施方案中，INHBE dsRNA藥劑與遞送劑連接。

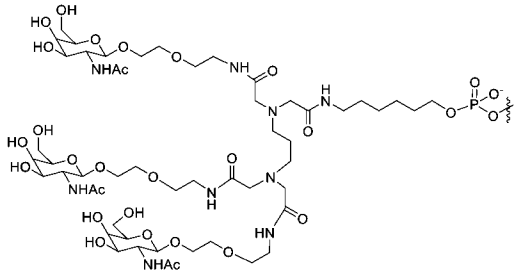
【0175】 可用於將INHBE dsRNA藥劑遞送至細胞、組織和/或受試者的方法的非限制性示例包括：INHBE dsRNA-GalNAc綴合物、SAMiRNA技術、基於LNP的遞送方法，以及裸RNA遞送。這些遞送方法和其他遞送方法已在本領域成功用於遞送治療性RNAi藥劑以治療各種疾病和病症，諸如但不限於：肝病、急性間歇性卟啉病（AIP）、血友病、肺纖維化等。各種遞送方式的細節可參見出版物，諸如：Nikam, R.R.和K. R. Gore (2018) Nucleic Acid Ther, 28 (4), 209-224 Aug 2018；Springer A.D.和S.F.Dowdy (2018) Nucleic Acid Ther.Jun 1; 28(3): 109–118；Lee, K.等人，(2018) Arch Pharm Res, 41(9), 867-874；以及Nair, J.K.等人，(2014) J. Am.

Chem.Soc.136:16958-16961，這些文獻中的每一篇的內容以引用方式併入本文。

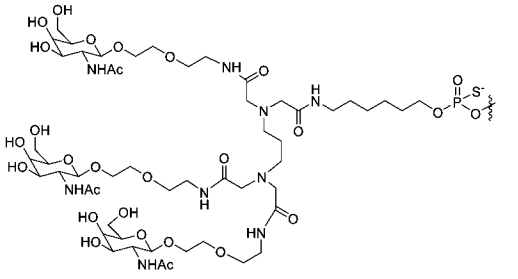
【0176】 本發明的一些實施方案包括使用脂質奈米顆粒（LNP）將本發明的INHBE dsRNA藥劑遞送至細胞、組織和/或受試者。LNP通常用於在體內遞送INHBE dsRNA藥劑，包括治療性INHBE dsRNA藥劑。使用LNP或其他遞送劑的一個益處是當使用該LNP或其他遞送劑將INHBE RNA藥劑遞送至受試者時，INHBE RNA藥劑的穩定性增強。在本發明的一些實施方案中，LNP包括負載有一種或多種本發明的INHBE RNAi分子的陽離子LNP。將包含INHBE RNAi分子的LNP施用於受試者，該LNP及其所連接的INHBE RNAi分子經由胞吞作用被細胞攝取，它們的存在導致RNAi觸發分子的釋放，從而介導RNAi。

【0177】 可用於本發明的實施方案中以將本發明的INHBE dsRNA藥劑遞送至細胞、組織和/或受試者的遞送劑的另一個非限制性示例是包含GalNAc的藥劑，該遞送劑與本發明的INHBE dsRNA藥劑連接並將INHBE dsRNA藥劑遞送至細胞、組織和/或受試者。可用於本發明的方法和組合物的某些實施方案中的某些包含GalNAc的遞送劑的附加示例公開於PCT申請：WO2020191183A1（其全文併入本文）。可用於本發明的組合物和方法中以將INHBE dsRNA藥劑遞送至細胞的GalNAc靶向配體的非限制性示例是靶向配體簇。本文所呈現的靶向配體簇的示例稱為：具有磷酸二酯鍵（GLO）的GalNAc配體和具有硫代磷酸酯鍵（GLS）的GalNAc配體。術語“GLX-n”在本文可用於表示所連接的含GalNAc的化合物是以下化合物中的任一者：GLS-1*、GLS-2*、GLS-3*、GLS-4*、GLS-5*、GLS-6*、

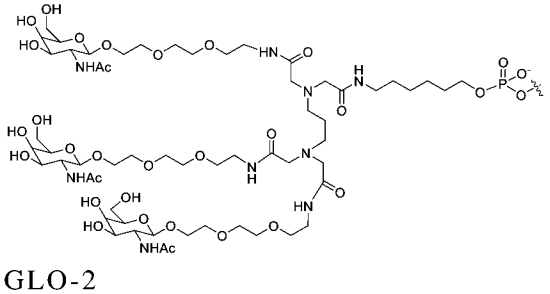
GLS-7*、GLS-8*、GLS-9*、GLS-10*、GLS-11*、GLS-12*、GLS-13*、GLS-14*、GLS-15*、GLS-16*、GLO-1、GLO-2、GLO-3、GLO-4、GLO-5、GLO-6、GLO-7、GLO-8、GLO-9、GLO-10、GLO-11、GLO-12、GLO-13、GLO-14、GLO-15和GLO-16，這些化合物中的每一者的結構示於下文，並且下文具有GalNAc靶向配體與本發明的RNAi藥劑的連接位置，位於上述每一者的最右側（以“≀”顯示）。應當理解，本發明的任何RNAi和dsRNA分子可與下文所示的GLS-1*、GLS-2*、GLS-3*、GLS-4*、GLS-5*、GLS-6*、GLS-7*、GLS-8*、GLS-9*、GLS-10*、GLS-11*、GLS-12*、GLS-13*、GLS-14*、GLS-15*、GLS-16*、GLO-1、GLO-2、GLO-3、GLO-4、GLO-5、GLO-6、GLO-7、GLO-8、GLO-9、GLO-10、GLO-11、GLO-12、GLO-13、GLO-14、GLO-15和GLO-16、GLO-1至GLO-16以及GLS-1*至GLS-16*連接。



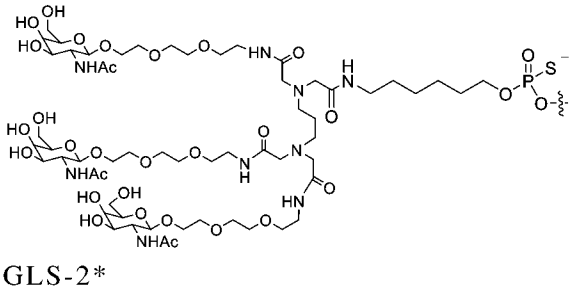
GLO-1



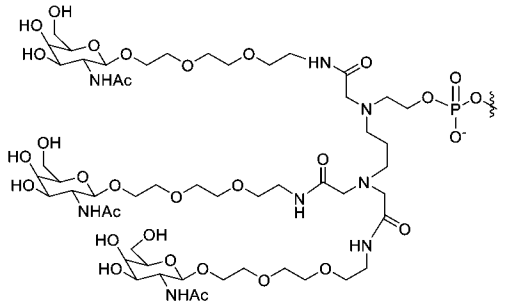
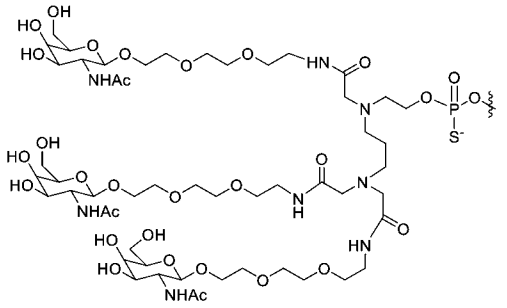
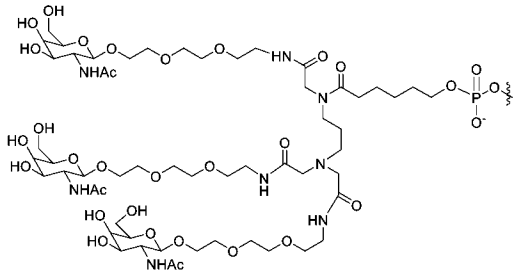
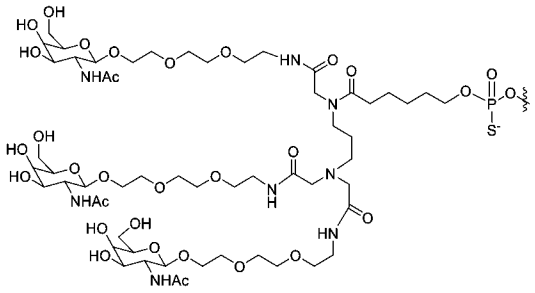
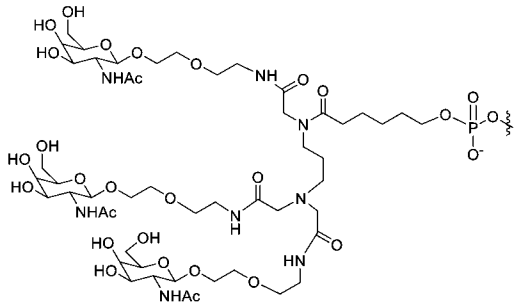
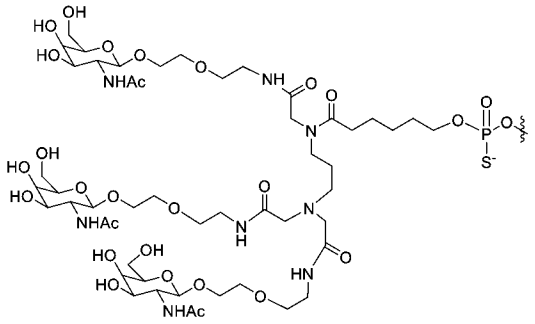
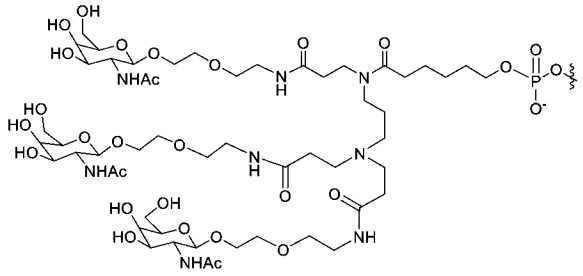
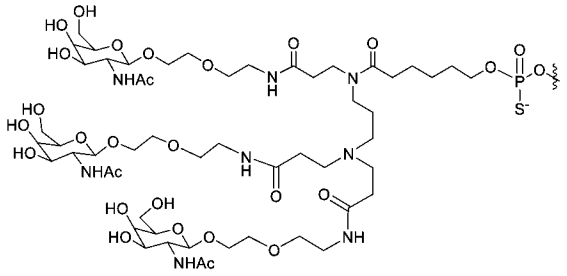
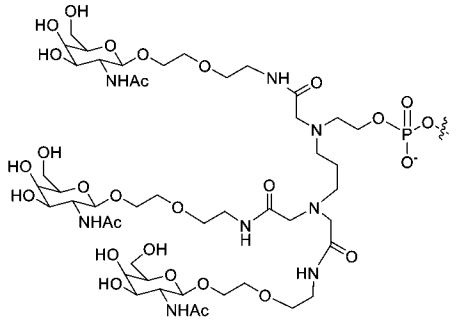
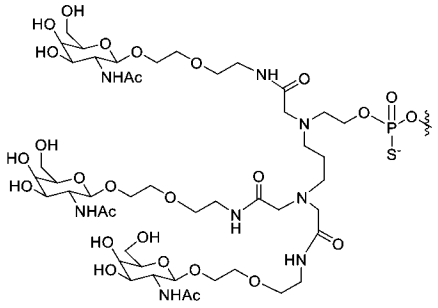
GLS-1*

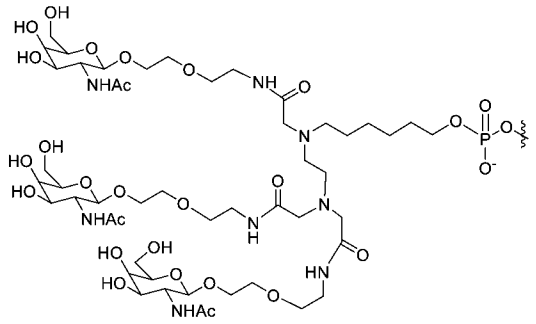
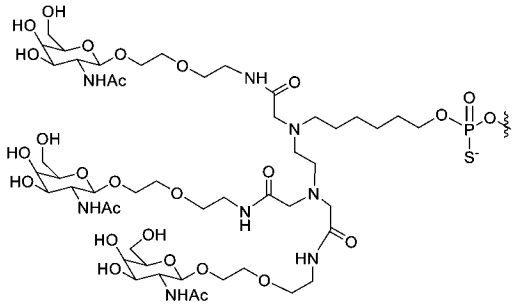
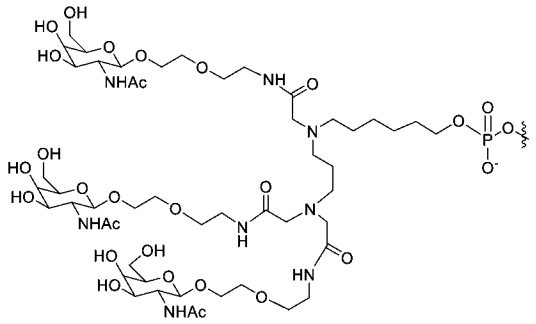
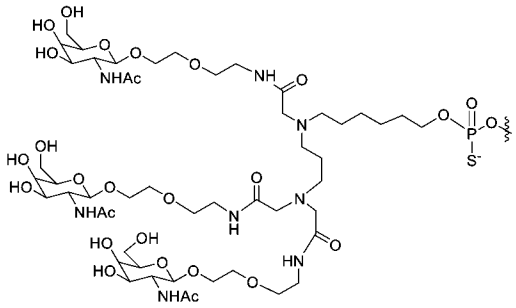
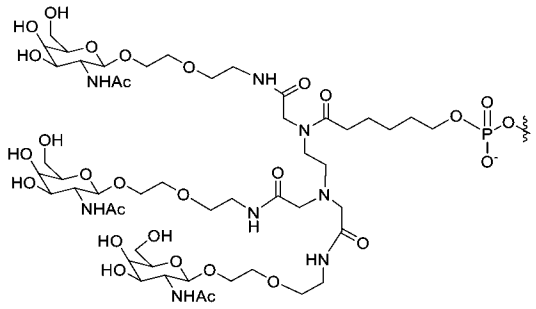
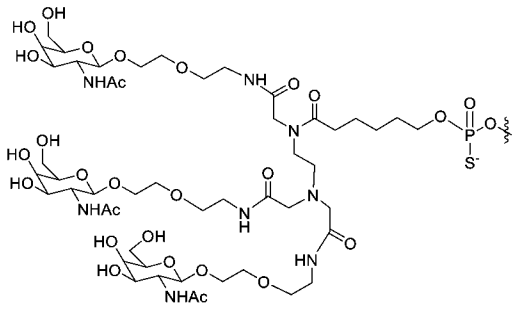
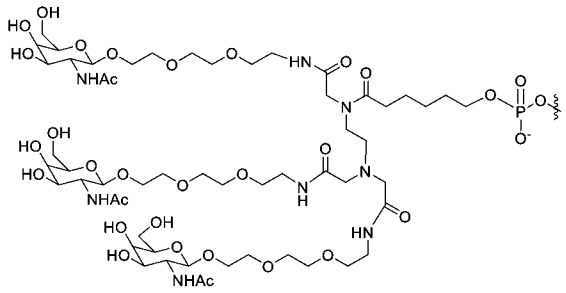
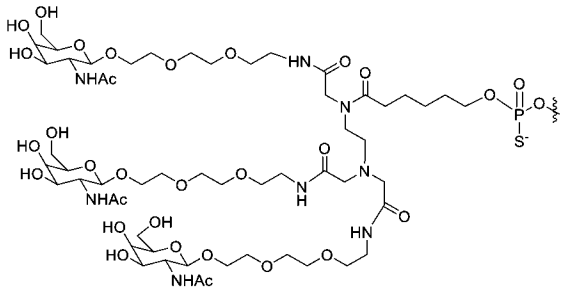
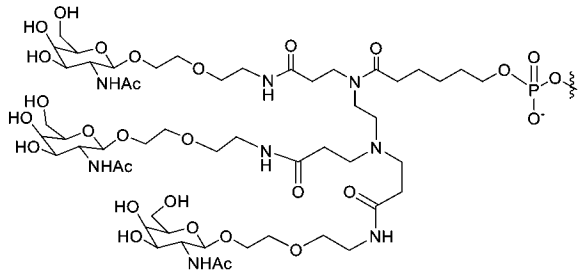
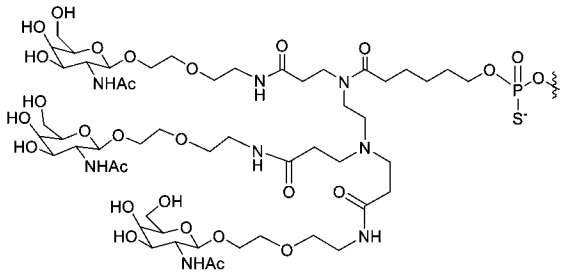


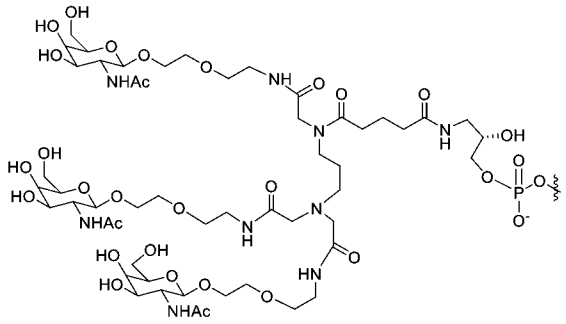
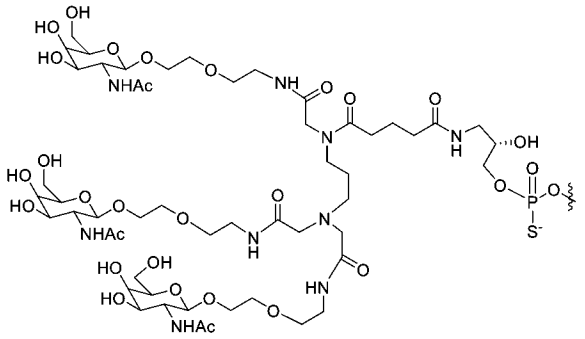
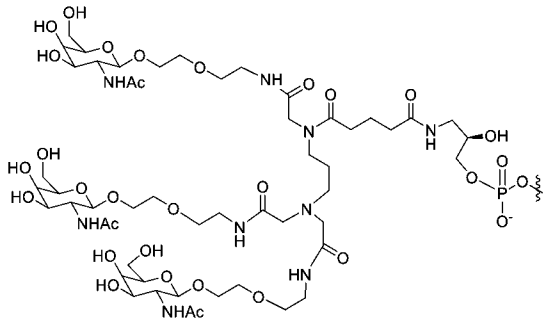
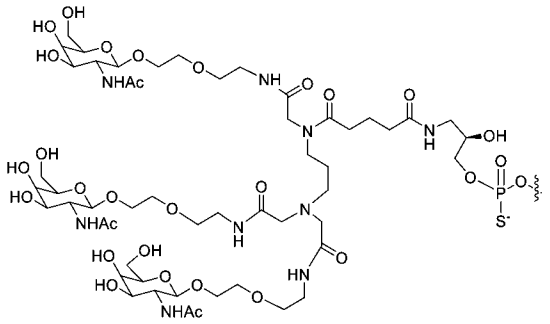
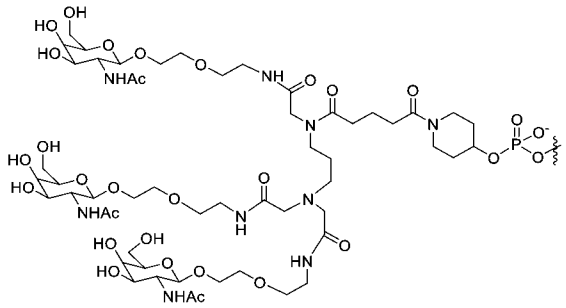
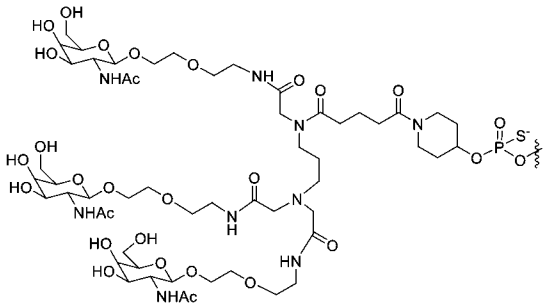
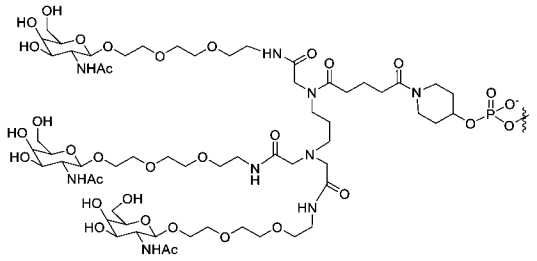
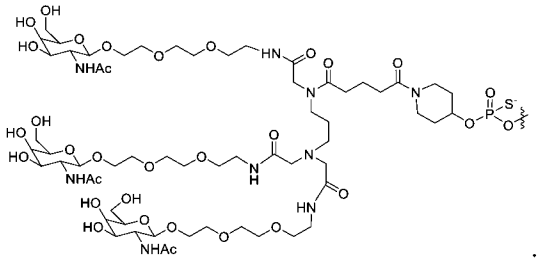
GLO-2



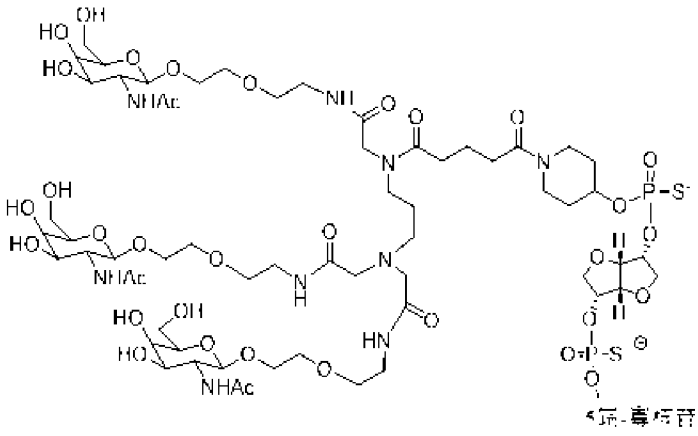
GLS-2*

 GLO-3	 GLS-3*
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*
 GLO-6	 GLS-6*
 GLO-7	 GLS-7*

 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*
 GLO-11	 GLS-11*
 GLO-12	 GLS-12*

 GLO-13	 GLS-13*
 GLO-14	 GLS-14*
 GLO-15	 GLS-15*
 GLO-16	 GLS-16*

【0178】在某些實施方案中，上述異甘露醇殘基可與一個或多個GalNAc靶向配體進一步綴合。與GalNAc靶向配體綴合的異甘露醇殘基的具體示例包括但不限於：



，其中短語“寡核苷酸”各自獨立地表示多核苷酸部分。

【0179】 在本發明的一些實施方案中，體內遞送還可以通過β-葡聚糖遞送系統進行，諸如描述於美國專利號5,032,401和5,607,677以及美國公開號2005/0281781中的那些，這些文獻據此以引用方式全文併入。還可使用本領域已知的方法，諸如電穿孔和脂質轉染法，在體外將INHBE RNAi藥劑引入細胞中。在本發明的方法的某些實施方案中，INHBE dsRNA可在沒有靶向劑的情況下遞送。這些RNA可作為“裸”RNA分子遞送。作為非限制性示例，本發明的INHBE dsRNA可以包含RNAi藥劑但不包含靶向劑（諸如GalNAc靶向化合物）的藥物組合物的形式施用於受試者，以治療受試者的INHBE相關疾病或病症，諸如心血管疾病。

【0180】 除了本文所述的某些遞送方式之外，應當理解，RNAi遞送方式（諸如但不限於本文所述的那些和本領域所使用的那些）可與本文所述的INHBE RNAi藥劑和治療方法的實施方案聯合使用。

【0181】 本發明的INHBE dsRNA藥劑可以有效降低細胞和/或受試者中的INHBE多肽水平和活性的量和方式施用於受試者。在本發明的方法的一些實施方案中，將一種或多種INHBE dsRNA藥劑施用於細胞和/或受

試者以治療與INHBE表達和活性相關的疾病或病症。在一些實施方案中，本發明的方法包括向需要此類治療的受試者施用一種或多種INHBE dsRNA藥劑，以減少該受試者的與INHBE表達相關的疾病或病症。可施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑以降低體外細胞、離體細胞和體內細胞中的一者或多者中的INHBE表達和/或活性。

【0182】 在本發明的一些實施方案中，通過將INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑遞送（例如，引入）至細胞中，降低了細胞中的INHBE多肽水平，並因此降低了該細胞中的INHBE多肽活性。靶向劑和方法可用於輔助將INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑遞送至受試者體內的特定細胞類型、細胞亞型、器官、空間區域，和/或遞送至細胞內的亞細胞區域。INHBE dsRNA藥劑可在本發明的某些方法中單獨施用或者與一種或多種附加INHBE dsRNA藥劑組合施用。在一些實施方案中，將2、3、4種或更多種獨立選擇的INHBE dsRNA藥劑施用於受試者。

【0183】 在本發明的某些實施方案中，將INHBE dsRNA藥劑和與一種或多種治療INHBE相關疾病或病症的附加治療方案聯合施用於受試者以治療該INHBE相關疾病或病症。附加治療方案的非限制性示例是：施用一種或多種本發明的INHBE反義多核苷酸，施用非INHBE dsRNA治療劑，以及行為矯正。可在以下時間中的一個或多個時間施用附加治療方案：在施用本發明的INHBE dsRNA藥劑之前、同時和之後。應當理解，如本文所用的同時，在時間零的5分鐘內，在時間零的10分鐘內，在時間零的30分鐘內，在時間零的45分鐘內以及在時間零的60分鐘內，其中“時間零”是將本發明的INHBE dsRNA藥劑施用於受試者的時間。非INHBE dsRNA治療劑

的非限制性示例是ACE抑制劑。這些治療劑和其他治療劑以及行為矯正是本領域已知的，並且用於治療受試者的INHBE相關疾病或病症，並且可與一種或多種本發明的INHBE dsRNA藥劑的施用組合而施用於受試者以治療INHBE相關疾病或病症。施用於細胞或受試者以治療INHBE相關疾病或病症的本發明的INHBE dsRNA藥劑可以協同方式與一種或多種其他治療劑或治療性活動作用，並增強該一種或多種治療劑或活性劑的有效性和/或增強該INHBE dsRNA藥劑在治療該INHBE相關疾病或病症方面的有效性。

【0184】 本發明的包括施用INHBE dsRNA藥劑的治療方法可在以下時間使用：在INHBE相關疾病或病症發作之前和/或當INHBE相關疾病或病症存在時，包括該疾病或病症的早期、中期和晚期以及在這些階段中的任一者之前和之後的所有時間。本發明的方法還可用於治療先前已用一種或多種其他治療劑和/或治療性活動治療過的患有治療INHBE相關疾病或病症的受試者，這些治療劑和/或治療性活動在治療該受試者的INHBE相關疾病或病症方面不成功、最低限度地成功和/或不再成功。

載體編碼的dsRNA

【0185】 在本發明的某些實施方案中，可使用載體將INHBE dsRNA藥劑遞送至細胞中。INHBE dsRNA藥劑轉錄單元可包含在DNA或RNA載體中。製備和使用此類編碼轉基因的載體以將序列遞送至細胞和/或受試者中是本領域熟知的。載體可用於本發明的導致INHBE dsRNA瞬時表達的方法中，例如達至少1小時、2小時、3小時、4小時、5小時、6小時、7小時、

8小時、9小時、10小時或更多小時，1周、2周、3周、4周、5周、6周、7周、8周、9周、10周或更多周。瞬時表達的時長可使用基於元件（諸如但不限於所選的特定載體構建體以及靶細胞和/或組織）的常規方法來測定。此類轉基因可作為線性構建體、環狀質粒或病毒載體引入，該病毒載體可以是整合載體或非整合載體。轉基因還可被構建成使其作為染色體外質粒遺傳（Gassmann等人，Proc.Natl.Acad.Sci.USA (1995) 92:1292）。

【0186】 INHBE dsRNA藥劑的一條或多條單鏈可由表達載體上的啟動子轉錄。當表達兩條單獨的鏈以產生例如dsRNA時，可使用諸如轉染或感染的方式將兩個單獨的表達載體共同引入細胞中。在某些實施方案中，本發明的INHBE dsRNA藥劑的每條單獨的鏈可由均包括在相同表達載體上的啟動子轉錄。在本發明的某些實施方案中，INHBE dsRNA藥劑被表達為通過接頭多核苷酸序列接合的反向重複多核苷酸，使得INHBE dsRNA藥劑具有莖環結構。

【0187】 RNA表達載體的非限制性示例是DNA質粒或病毒載體。可用於本發明實施方案的表達載體可與真核細胞相容。真核細胞表達載體是本領域常規使用的，並且可從多種商業來源獲得。對表達INHBE dsRNA的載體的遞送可以是全身性的，諸如通過靜脈內或肌內施用，通過施用於從受試者體內移植隨後重新引入受試者體內的靶細胞，或者通過任何其他允許引入期望的靶細胞中的方式。

【0188】 可包含在本發明的方法的實施方案中的病毒載體系統包括但不限於(a)腺病毒載體；(b)逆轉錄病毒載體，包括但不限於慢病毒載體、莫洛尼鼠白血病病毒等；(c)腺相關病毒載體；(d)單純皰疹病毒載體；(e)SV

40載體；(f)多瘤病毒載體；(g)乳頭狀瘤病毒載體；(h)小核糖核酸病毒載體；(i)痘病毒載體，諸如正痘病毒，例如牛痘病毒載體或禽痘，例如金絲雀痘或雞痘；和(j)輔助依賴性腺病毒或無宿主腺病毒。用於INHBE dsRNA藥劑的重組表達的構建體可包括調控元件，諸如啟動子、增強子等，其可被選擇來提供組成型或調控型/誘導型表達。病毒載體系統以及啟動子和增強子的使用等是本領域常規的，並且可與本文所述的方法和組合物聯合使用。

【0189】 本發明的某些實施方案包括使用病毒載體將INHBE dsRNA藥劑遞送至細胞中。許多基於腺病毒的遞送系統在本領域中常規用於遞送至例如肺、肝、中樞神經系統、內皮細胞和肌肉中。可用於本發明的方法的病毒載體的非限制性示例是：AAV載體、痘病毒諸如牛痘病毒、改良的安卡拉病毒（MVA）、NYVAC、禽痘諸如雞痘或金絲雀痘。

【0190】 本發明的某些實施方案包括使用載體將INHBE dsRNA藥劑遞送至細胞中的方法，並且此類載體可位於藥學上可接受的載劑中，該藥學上可接受的載劑可以但不必包括其中包埋有基因遞送媒介物的緩釋基質。在一些實施方案中，用於遞送INHBE dsRNA的載體可由重組細胞產生，並且本發明的藥物組合物可包括一種或多種產生INHBE dsRNA遞送系統的細胞。

含有INHBE dsRNA或ssRNA藥劑的藥物組合物

【0191】 本發明的某些實施方案包括使用含有INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑和藥學上可接受的載劑的藥物組合物。含有

INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的藥物組合物可用於本發明的方法中以降低細胞中的INHBE基因表達和INHBE活性，並且可用於治療INHBE相關疾病或病症。此類藥物組合物可基於遞送模式來配製。用於遞送模式的製劑的非限制性示例是：被配製用於皮下遞送的組合物、被配製用於經由腸胃外遞送的全身性施用的組合物、被配製用於靜脈內（IV）遞送的組合物、被配製用於鞘內遞送的組合物、被配製用於眼內遞送的組合物等。施用本發明的藥物組合物以將INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑遞送至細胞中可使用一種或多種方法進行，諸如：局部（例如通過經皮貼劑）、肺部（例如通過吸入或吹入粉末或氣溶膠，包括通過噴霧器）、氣管內、鼻內、表皮和經皮、口服或腸胃外施用。腸胃外施用包括靜脈內、動脈內、皮下、腹膜內或肌內注射或輸注；皮下施用，例如經由植入裝置；或顱內施用，例如通過實質內、鞘內或心室內施用。INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑還可直接遞送至靶組織中，例如直接遞送至肝臟中。應當理解，“遞送INHBE dsRNA藥劑”或“遞送INHBE反義多核苷酸藥劑”進入細胞涵蓋分別直接遞送INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑，以及在細胞中由遞送至細胞中的編碼載體表達INHBE dsRNA藥劑，或者通過任何合適的方式使INHBE dsRNA或INHBE反義多核苷酸藥劑存在於細胞中。製劑的製備和使用以及用於遞送抑制性RNA的方式是本領域熟知的且常規使用的。

【0192】 如本文所用，“藥物組合物”包含藥理學有效量的本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑和藥學上可接受的載劑。術語“藥學上可接受的載劑”是指用於施用治療劑的載劑。此類載劑包括但

不限於鹽水、緩衝鹽水、右旋糖、水、甘油、乙醇以及它們的組合。該術語特別排除細胞培養基。對於口服施用的藥物，藥學上可接受的載劑包括但不限於藥學上可接受的賦形劑，諸如惰性稀釋劑、崩解劑、黏合劑、潤滑劑、甜味劑、調味劑、著色劑和防腐劑。合適的惰性稀釋劑包括碳酸鈉和碳酸鈣、磷酸鈉和磷酸鈣以及乳糖，同時玉米澱粉和海藻酸是合適的崩解劑。黏合劑可包括澱粉和明膠，同時潤滑劑（如果存在）通常是硬脂酸鎂、硬脂酸或滑石。如果需要，片劑可用諸如單硬脂酸甘油酯或二硬脂酸甘油酯的材料包衣，以延遲在胃腸道中的吸收。包含在藥物製劑中的藥劑在下文中進一步描述。

【0193】 如本文所用，術語諸如“藥理學有效量”、“治療有效量”和“有效量”是指產生預期的藥理學、治療性或預防性結果的本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的量。例如，如果給定的臨床治療在與疾病或障礙相關的可測量參數降低至少10%時被認為是有效的，則用於治療該疾病或障礙的藥物的治療有效量是使該參數降低至少10%所必需的量。例如，治療有效量的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可使INHBE多肽水平降低至少10%。

有效量

【0194】 本發明的方法在某些方面包括使細胞與有效量的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑接觸，以降低所接觸的細胞中的INHBE基因表達。本發明的方法的某些實施方案包括將INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑以有效降低受試者中的INHBE基因表達且

治療INHBE相關疾病或病症的量施用於受試者。就降低INHBE的表達和/或治療INHBE相關疾病或病症而言，所使用的“有效量”是實現期望的生物學效應所必需或足夠的量。例如，治療INHBE相關疾病或病症的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的有效量可以是(i)減緩或停止疾病或病症的進展；或(ii)逆轉、減輕或消除該疾病或病症的一種或多種症狀所必需的量。在本發明的一些方面，有效量是當施用於需要治療INHBE相關疾病或病症的受試者時產生預防和/或治療該疾病或病症的治療反應的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的量。根據本發明的一些方面，有效量是當與用於INHBE相關疾病或病症的另一種治療性處理組合或共同施用時產生預防和/或治療該疾病或病症的治療反應的本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的量。在本發明的一些實施方案中，用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑治療受試者的生物學效應可以是改善和或絕對消除由INHBE相關疾病或病症引起的症狀。在本發明的一些實施方案中，生物學效應是指INHBE相關疾病或病症的完全消除，例如通過指示受試者沒有INHBE相關疾病或病症的診斷測試來證明。可檢測的生理症狀的非限制性示例包括在施用本發明的藥劑後受試者肝臟中INHBE水平的降低。可使用本領域已知的其他評估INHBE相關疾病或病症的狀態的方式來測定本發明的藥物和/或方法對INHBE相關疾病或病症的效果。

【0195】 典型地，將在臨床試驗中測定將INHBE多肽活性降低至治療INHBE相關疾病或病症的水平的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的有效量，從而在盲法研究中建立測試群體與對照群體的有效劑

量。在一些實施方案中，有效量將是產生期望反應的量，例如，減輕患有INHBE相關疾病或病症的細胞、組織和/或受試者中的該疾病或病症的量。因此，用於治療可通過降低INHBE多肽活性來治療的INHBE相關疾病或病症的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的有效量可以是這樣的量：在施用時將受試者中INHBE多肽活性的量降低至低於在沒有施用INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的情況下存在於細胞、組織和/或受試者中的量的量。在本發明的某些方面，在未接觸或未施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的細胞、組織和/或受試者中存在的INHBE多肽活性和/或INHBE基因表達的水平被稱為“對照”量。在本發明的方法的一些實施方案中，受試者的對照量是受試者的治療前量，換句話說，在施用INHBE藥劑之前受試者中的水平可以是該受試者的對照水平，並與在將siRNA施用於該受試者之後受試者體內INHBE多肽活性和/或INHBE基因表達的水平進行比較。在治療INHBE相關疾病或病症的情況下，期望反應可以是減輕或消除細胞、組織和/或受試者的疾病或病症的一種或多種症狀。鈣降低或消除可以是暫時的，或者可以是永久的。應當理解，INHBE相關疾病或病症的狀態可使用測定INHBE多肽活性、INHBE基因表達、症狀評估、臨床試驗等的方法來監測。在本發明的一些方面，對與INHBE相關的疾病或病症的治療的期望反應是延遲或者甚至預防該疾病或病症的發作。

【0196】降低INHBE多肽活性的化合物的有效量還可通過評估INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的施用對細胞或受試者的生理效應（諸如INHBE相關疾病或病症在施用後的減輕）來測定。對受試

者的分析和/或症狀監測可用於測定可以本發明的藥物化合物形式施用的本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的功效，並且用於測定存在或不存在對治療的反應。非限制性示例是一種或多種本領域已知的INHBE生物活性降低測試，例如，或與INHBE水平升高（優選在血液或血清中）相關的其他病理學。

【0197】 本發明的一些實施方案包括通過評估和/或監測受試者的INHBE相關疾病或病症的一種或多種“生理特徵”來測定施用於該受試者的本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑治療該INHBE相關疾病或病症的功效的方法。INHBE相關疾病或病症的生理特徵的非限制性示例是受試者的INHBE mRNA水平、INHBE蛋白水平或根據體重指數調整的腰臀比。

【0198】 應當理解，至少部分地基於針對受試者測定的疾病和/或病症狀態和/或生理特徵的此類測定結果，可改變施用於該受試者的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的量。治療量可有所變化，例如通過增加或減少INHBE-dsRNA藥劑或INHBE反義多核苷酸藥劑的量，通過改變其中分別施用INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的組合物，通過改變施用途徑，通過改變施用時間等。INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的有效量將隨以下項而變化：所治療的特定病症、所治療的受試者的年齡和身體狀況、病症的嚴重程度、治療的持續時間、同步治療（如果有的話）的性質、具體的施用途徑以及醫療保健人員的知識和專業技能範圍的其他因素。例如，有效量可取決於有效治療INHBE相關疾病或病症的INHBE多肽活性和/或INHBE基因表達的期望水

平。技術人員可憑經驗確定用於本發明方法的本發明的特定INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的有效量，而不需要進行過多的實驗。與本文所提供的教導內容結合，通過從本發明的各種INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑中進行選擇，以及權衡諸如效力、相對生物利用度、患者體重、不良副作用的嚴重程度和優選的施用模式等因素，可制定有效治療特定受試者的有效預防性或治療性處理方案。如本發明的實施方案中使用的，本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的有效量可以是當與細胞接觸時在細胞中產生期望的生物學效應的量。

【0199】 應當認識到，INHBE基因沉默可通過任何表達INHBE的細胞（無論是組成型還是通過基因組工程型）和任何適當的分析來測定。在本發明的一些實施方案中，通過施用本發明的INHBE dsRNA藥劑，INHBE基因表達降低至少5%、6%、7%、8%、9%、10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、95%或100%。在本發明的一些實施方案中，通過施用本發明的INHBE dsRNA藥劑，INHBE基因表達降低5%至10%、5%至25%、10%至50%、10%至75%、25%至75%、25%至100%或50%至100%。

給藥

【0200】 INHBE dsRNA藥劑和INHBE反義多核苷酸藥劑在藥物組合物中以足以抑制INHBE基因表達的劑量遞送。在本發明的某些實施方案中，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的劑量在每天0.01毫克/千克接受者體重至200.0毫克/千克接受者體重的範圍內，通常在每天

1mg/kg體重至50mg/kg體重、5mg/kg體重至40mg/kg體重、10mg/kg體重至30mg/kg體重、1mg/kg體重至20mg/kg體重、1mg/kg體重至10mg/kg體重、4mg/kg體重至15mg/kg體重的範圍內，包括端值。例如，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可以每次單劑量約0.01mg/kg、0.05mg/kg、0.1mg/kg、0.2mg/kg、0.3mg/kg、0.4mg/kg、0.5mg/kg、1mg/kg、1.1mg/kg、1.2mg/kg、1.3mg/kg、1.4mg/kg、1.5mg/kg、1.6mg/kg、1.7mg/kg、1.8mg/kg、1.9mg/kg、2mg/kg、2.1mg/kg、2.2mg/kg、2.3mg/kg、2.4mg/kg、2.5mg/kg、2.6mg/kg、2.7mg/kg、2.8mg/kg、2.9mg/kg、3.0mg/kg、3.1mg/kg、3.2mg/kg、3.3mg/kg、3.4mg/kg、3.5mg/kg、3.6mg/kg、3.7mg/kg、3.8mg/kg、3.9mg/kg、4mg/kg、4.1mg/kg、4.2mg/kg、4.3mg/kg、4.4mg/kg、4.5mg/kg、4.6mg/kg、4.7mg/kg、4.8mg/kg、4.9mg/kg、5mg/kg、5.1mg/kg、5.2mg/kg、5.3mg/kg、5.4mg/kg、5.5mg/kg、5.6mg/kg、5.7mg/kg、5.8mg/kg、5.9mg/kg、6mg/kg、6.1mg/kg、6.2mg/kg、6.3mg/kg、6.4mg/kg、6.5mg/kg、6.6mg/kg、6.7mg/kg、6.8mg/kg、6.9mg/kg、7mg/kg、7.1mg/kg、7.2mg/kg、7.3mg/kg、7.4mg/kg、7.5mg/kg、7.6mg/kg、7.7mg/kg、7.8mg/kg、7.9mg/kg、8mg/kg、8.1mg/kg、8.2mg/kg、8.3mg/kg、8.4mg/kg、8.5mg/kg、8.6mg/kg、8.7mg/kg、8.8mg/kg、8.9mg/kg、9mg/kg、9.1mg/kg、9.2mg/kg、9.3mg/kg、9.4mg/kg、9.5mg/kg、9.6mg/kg、9.7mg/kg、9.8mg/kg、9.9mg/kg、10mg/kg、11mg/kg、12mg/kg、13mg/kg、14mg/kg、15mg/kg、16mg/kg、17mg/kg、18mg/kg、19mg/kg、20mg/kg、21mg/kg、22mg/kg、23mg/kg、24mg/kg、25mg/kg、26mg/kg、27mg/kg、28mg/kg、29mg/kg、30mg/kg、31mg/kg、32mg/kg、33mg/kg、34mg/kg、35mg/kg、36mg/kg、37mg/kg、38mg/kg、39mg/kg、40mg/kg、

41mg/kg、42mg/kg、43mg/kg、44mg/kg、45mg/kg、46mg/kg、47mg/kg、48mg/kg、49mg/kg至50mg/kg體重的量施用。

【0201】 在確定本發明的INHBE dsRNA藥劑的劑量和遞送時間時，可考慮多種因素。所遞送的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的絕對量將取決於多種因素，包括同步治療、劑量數量和個體受試者參數，包括年齡、身體狀況、身高和體重。這些因素是本領域普通技術人員熟知的因素，並且僅通過常規實驗就可解決。在一些實施方案中，可使用最大劑量，即，根據合理醫學判斷的最高安全劑量。

【0202】 在一些實施方案中，本發明的方法可包括向受試者施用1、2、3、4、5、6、7、8、9、10次或更多次劑量的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑。在一些情況下，可至少每天、每隔一天、每週、每隔一周、每月等向受試者施用藥物化合物（例如，包含INHBE dsRNA藥劑或包含INHBE反義多核苷酸藥劑）。劑量可每天施用一次或每天施用多次，例如，在一個24小時的時間段內施用2、3、4、5次或更多次。本發明的藥物組合物可每天施用一次，或者INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可作為兩次、三次或更多次亞劑量在全天以適當的間隔施用，或者甚至使用持續輸注或通過控釋製劑遞送。在本發明的方法的一些實施方案中，將本發明的藥物組合物以每天一次或多次、每週一次或多次、每月一次或多次或每年一次或多次施用於受試者。

【0203】 在一些方面，本發明的方法包括單獨施用藥用化合物，與一種或多種其他INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑組合該施用藥用化合物，和/或與施用於患有INHBE相關疾病或病症的受試者的其他藥

物療法或治療活動或方案組合施用該藥用化合物。藥物化合物可以藥物組合物的形式施用。本發明的方法中使用的藥物組合物可以是無菌的，並且含有一定量的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑，該INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑將使INHBE多肽的活性降低至足以在適於施用於受試者的單位重量或體積內產生期望反應的水平。施用於受試者的包含降低INHBE蛋白活性的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的藥物組合物的劑量可根據不同參數進行選擇，特別是根據所使用的施用模式和受試者的狀態進行選擇。其他因素包括期望的治療時間。如果在施加的初始劑量下受試者的反應不足，則可在患者耐受性允許的範圍內採用更高的劑量（或者通過不同的、更局部的遞送途徑來有效提高劑量）。

治療

【0204】 如本文所用，“INHBE相關疾病”、“INHBE相關疾病和病症”和“由INHBE引起和/或調節的疾病和病症”包括與INHBE基因或蛋白相關的任何疾病。此類疾病可能是由以下原因引起的：例如，INHBE蛋白的過量產生、INHBE基因的突變、INHBE蛋白的異常切割、INHBE與其他蛋白質或其他內源性或外源性物質之間的異常相互作用。示例性的INHBE相關疾病包括但不限於：2型糖尿病、肥胖症（特別是腹部肥胖症）、脂肪代謝障礙（諸如無法在區域性脂肪庫中沉積脂肪（部分脂肪代謝障礙）或者無法在全身沉積脂肪（脂肪萎縮））、肝臟脂肪沉積或脂肪肝病及其併發症（諸如，例如肝硬化、纖維化或肝臟炎症）、高脂血症或血脂異常（低密

度脂蛋白膽固醇（LDL-C）、甘油三酯、極低密度脂蛋白膽固醇（VLDL-C）、載脂蛋白B或其他脂質成分的循環水平高或改變）、肝酶水平或其他肝損傷標誌物（諸如，例如ALT和/或AST）較高或升高或改變、非酒精性脂肪性肝炎（NASH）、胰島素抵抗或者在空腹或代謝挑戰期間的胰島素水平較高或改變、其他類型的肝臟炎症和/或甘油三酯水平升高，和/或心血管疾病，諸如心肌病、心力衰竭，以及高血壓和/或高血壓症、血糖或葡萄糖較高或高血糖症、代謝症候群、冠狀動脈疾病和其他冠狀動脈粥樣硬化病症，以及上述病症中的每一者的併發症。

【0205】 如本文所用，“症狀”或“標誌”意指指示疾病或障礙的存在或程度的任何身體特徵或測試結果。在某些實施方案中，症狀對於受試者或檢查或測試該受試者的醫學專業人員來說是顯而易見的。在某些實施方案中，在進行侵入性診斷測試時，標誌是顯而易見的，包括但不限於受試者的根據體重指數調整的腰臀比。鑒定與更有利的脂肪分佈（諸如較低的WHR，特別是當針對BMI進行校正時）相關的遺傳變體，可作為一種鑒定在治療這些心臟代謝疾病中可帶來獲益的機制的途徑。

【0206】 在本發明的某些方面，可在診斷INHBE相關疾病或病症之前或之後的一個或多個時間，向受試者施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑。在本發明的一些方面，受試者處於患有或發展INHBE相關疾病或病症的風險中。處於發展INHBE相關疾病或病症的風險中的受試者是與發展INHBE相關疾病或病症的控制風險相比，發展INHBE相關疾病或病症的可能性增加的受試者。在本發明的一些實施方案中，與控制風險水平相比的風險水平可以是統計學上顯著的。處於風險中的受試

者可包括，例如，已經患有或者將患有預先存在的疾病和/或遺傳異常的受試者，該疾病和/或遺傳異常使該受試者比未患有該預先存在的疾病或遺傳異常的對照受試者更容易患上INHBE相關疾病或病症；具有INHBE相關疾病或病症的家族和/或個人病史的受試者；和先前已接受INHBE相關疾病或病症治療的受試者。應當理解，使受試者更容易患上INHBE相關疾病或病症的預先存在的疾病和/或遺傳異常，可以是當存在時先前已被鑒定為與發展INHBE相關疾病或病症的較高可能性具有相關關係的疾病或遺傳異常。

【0207】 應當理解，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可基於個體受試者的醫學狀態而施用於受試者。例如，為受試者提供的醫療保健可評估在從受試者獲得的樣本中測量的INHBE水平，並確定通過施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑來降低受試者的INHBE水平是合乎期望的。在該示例中，即使受試者未被診斷為患有INHBE相關疾病，諸如本文公開的疾病，INHBE水平也可被認為是INHBE相關病症的生理特徵。醫療保健提供者可監測受試者INHBE水平的變化，作為施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的功效的衡量標準。在一個非限制性示例中，可從受試者獲得生物樣本，諸如血液或血清樣本，並在樣本中測定受試者的INHBE水平。將INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑施用於受試者，並在施用後從受試者獲得血液樣本，使用該樣本測定INHBE水平，並將結果與受試者的施用前（之前）樣本中測定的結果進行比較。與施用前水平相比，受試者的INHBE水平在施用後樣本中的降低表明所施用的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑在降低受試者中的脂質水平方面有效。本發明的方法的某些實施

方案包括調整治療，包括至少部分地基於對由該治療引起的INHBE相關疾病或病症的一種或多種受試者生理特徵變化的評估，來向受試者施用本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑。例如，在本發明的一些實施方案中，可為受試者測定所施用的本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑的效果，並用於輔助調整隨後施用於受試者的本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑的量。在一個非限制性示例中，向受試者施用本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑，在施用後測定受試者的INHBE水平，並且至少部分地基於所測定的水平，確定需要更大量的dsRNA藥劑或INHBE反義多核苷酸藥劑以增加所施用的藥劑的生理效應，例如降低或進一步降低受試者的INHBE水平。在另一個非限制性示例中，向受試者施用本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑，在施用後測定受試者的INHBE水平，並且至少部分地基於所測定的水平，確定需要向受試者施用較低量的dsRNA藥劑或INHBE反義多核苷酸藥劑。

【0208】 因此，本發明的一些實施方案包括對由受試者的先前治療引起的一種或多種生理特徵變化的評估，以用於調整隨後施用於該受試者的本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑的量。本發明的方法的一些實施方案包括對INHBE相關疾病或病症的生理特徵的1、2、3、4、5、6個或更多個測定結果，以評估和/或監測所施用的本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的功效，並任選地使用這些測定結果來調整以下項中的一者或多者：本發明的dsRNA藥劑或INHBE反義多核苷酸藥劑的劑量、施用方案和/或施用頻率，從而治療受試者的INHBE相關疾病或病症。在本發明的方法的一些實施方案中，向受試者施用有效量的本發明

的dsRNA藥劑或INHBE反義多核苷酸藥劑的期望結果是降低受試者的INHBE mRNA水平、受試者的INHBE蛋白水平或受試者的腰臀比。

【0209】 如本文所用，術語“治療”、“治療的”或“治療”當用於INHBE相關疾病或病症方面時，可以指降低受試者發展INHBE相關疾病或病症的可能性的預防性治療，並且還可以指在受試者已發展INHBE相關疾病或病症後的治療，以便消除或降低INHBE相關疾病或病症的水平，防止INHBE相關疾病或病症進一步惡化（例如，更嚴重），並且/或與缺少使受試者中的INHBE多肽活性降低的治療的受試者相比，減緩受試者的INHBE相關疾病或病症的進展。

【0210】 本發明的藥劑、組合物和方法的某些實施方案可用於抑制INHBE基因表達。如本文所用，關於INHBE基因表達的術語“抑制”、“沉默”、“降低”、“下調”和“敲低”意指INHBE基因的表達，如通過以下項中的一種或多種測量：當細胞、細胞組、組織、器官或受試者與本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑接觸（例如，用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑治療）時，與分別由INHBE基因轉錄的RNA對照水平、所表達的INHBE的活性水平或由mRNA翻譯的INHBE水平相比，在轉錄INHBE基因的細胞、細胞組、組織、器官或受試者中由基因轉錄的RNA水平、所表達的INHBE的活性水平和由mRNA翻譯的INHBE多肽、蛋白或蛋白亞基的水平均降低。在一些實施方案中，對照水平是在未接觸INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑（例如，未用該INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑治療）的細胞、組織、器官或受試者中的水平。

施用方法

【0211】INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的多種施用途徑可用於本發明的方法。所選的特定遞送模式將至少部分地取決於所治療的特定病症和治療功效所需的劑量。一般來講，本發明的方法可採用醫學上可接受的任何施用模式來實踐，意指對INHBE相關疾病或病症產生有效治療水平而不會引起臨床上無法接受的副作用的任何模式。在本發明的一些實施方案中，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可經由口服、腸內、黏膜、皮下和/或腸胃外途徑施用。術語“腸胃外”包括皮下、靜脈內、鞘內、肌內、腹膜內和胸骨內注射或輸注技術。其他途徑包括但不限於鼻腔（例如，經由胃鼻管）、皮膚、陰道、直腸、舌下和吸入。本發明的遞送途徑可包括鞘內、心室內或顱內。在本發明的一些實施方案中，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可置於緩釋基質內，並通過將該基質置於受試者體內進行施用。在本發明的一些方面，可使用包被有靶向特定細胞或細胞器的遞送劑的奈米顆粒將INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑遞送至受試者細胞。各種遞送方式、方法、藥劑是本領域已知的。遞送方法和遞送劑的非限制性示例另外提供於本文別處。在本發明的一些方面，關於INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的術語“遞送”可意指向細胞或受試者施用一種或多種“裸”INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑序列，並且在本發明的某些方面，“遞送”意指經由轉染方式向細胞或受試者施用，將包含INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的細胞遞送至受試者，將編碼INHBE dsRNA

藥劑或INHBE反義多核苷酸藥劑的載體遞送至細胞和/或受試者等。使用轉染方式遞送INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可包括向細胞和/或受試者施用載體。

【0212】 在本發明的一些方法中，一種或多種INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可以製劑形式施用，這些製劑可以藥學上可接受的溶液形式施用，這些藥學上可接受的溶液通常可含有藥學上可接受濃度的鹽、緩衝劑、防腐劑、相容的載劑、佐劑和任選的其他治療成分。在本發明的一些實施方案中，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可與另一種治療劑被配製用於同時施用。根據本發明的方法，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可以藥物組合物的形式施用。一般來講，藥物組合物包含INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑和任選的藥學上可接受的載劑。藥學上可接受的載劑是本領域普通技術人員熟知的。如本文所用，藥學上可接受的載劑意指不干擾活性成分的生物活性的有效性的無毒材料，該生物活性例如INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑在細胞或受試者中抑制INHBE基因表達的能力。施用和遞送dsRNA藥劑或INHBE反義多核苷酸藥劑以用於治療用途的許多方法是本領域已知的，並且可用於本發明的方法中。

【0213】 藥學上可接受的載劑包括稀釋劑、填充劑、鹽、緩衝劑、穩定劑、增溶劑和本領域熟知的其他物質。示例性的藥學上可接受的載劑描述於美國專利號5,211,657中，並且其他藥學上可接受的載劑是本領域技術人員已知的。此類製劑通常可含有鹽、緩衝劑、防腐劑、相容的載劑和任選的其他治療劑。當用於藥物時，鹽應當是藥學上可接受的鹽，但非藥學

上可接受的鹽也可方便地用於製備其藥學上可接受的鹽並且不排除在本發明的範圍之外。此類藥理學和藥學上可接受的鹽包括但不限於由以下酸製備的那些：鹽酸、氫溴酸、硫酸、硝酸、磷酸、馬來酸、乙酸、水楊酸、檸檬酸、甲酸、丙二酸、琥珀酸等。此外，藥學上可接受的鹽可被製備為鹼金屬鹽或鹼土金屬鹽，諸如鈉鹽、鉀鹽或鈣鹽。

【0214】 本發明的方法的一些實施方案包括直接向組織施用一種或多種INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑。在一些實施方案中，被施用化合物的組織是其中存在或可能出現INHBE相關疾病或病症的組織，該組織的非限制性示例是心臟。直接的組織施用可通過直接注射或其他方式實現。許多口服遞送的化合物自然地移動到肝臟並通過肝臟，並且本發明的治療方法的一些實施方案包括向受試者口服施用一種或多種INHBE dsRNA藥劑。INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑單獨施用或與其他治療劑聯合施用，可施用一次，或者另選地，它們可多次施用。如果多次施用，則INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可經由不同途徑施用。例如，儘管並非旨在進行限制，但第一次（或前幾次）施用可經由皮下方式進行，並且一次或多次附加施用可以是口服和/或全身性施用。在一些實施方案中，通過皮下將dsRNA藥劑施用於受試者。在某些實施方案中，通過靜脈內施用將dsRNA藥劑施用於受試者。在一些實施方案中，通過鞘內將dsRNA藥劑施用於受試者。在又一個實施方案中，通過腦池內將dsRNA藥劑施用於受試者。在某些實施方案中，dsRNA通過腦室內（ICV）注射、紋狀體內（IS）注射、靜脈內（IV）注射、皮下（SQ）注射或它們的組合施用。

【0215】對於本發明的期望全身性施用INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的實施方案，該INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可被配製用於通過注射施用，例如通過彈丸注射或持續輸注的腸胃外施用。注射用製劑可以單位劑型存在，例如在添加或未添加防腐劑的安瓿或多劑量容器中。INHBE dsRNA藥劑製劑（也稱為藥物組合物）可採取諸如在油性或水性媒介物中的懸浮液、溶液或乳液的形式，並且可含有配製劑，諸如懸浮劑、穩定劑和/或分散劑。

【0216】用於腸胃外施用的製劑包括無菌水性溶液或非水性溶液、懸浮液和乳液。非水性溶劑的示例是丙二醇、聚乙二醇、植物油（諸如橄欖油）和可注射的有機酯（諸如油酸乙酯）。水性載劑包括水、醇/水性溶液、乳液或懸浮液，包括鹽水和緩衝介質。腸胃外媒介物包括氯化鈉溶液、林格氏右旋糖、右旋糖和氯化鈉、乳酸林格氏液或固定油。靜脈內媒介物包括液體和營養補充劑、電解質補充劑（諸如基於林格氏右旋糖的補充劑）等。還可存在防腐劑和其他添加劑，諸如例如抗微生物劑、抗氧化劑、螯合劑和惰性氣體等。其他施用形式（諸如靜脈內施用）將導致較低的劑量。如果在施加的初始劑量下受試者的反應不足，則可在患者耐受性允許的範圍內採用更高的劑量（或者通過不同的、更局部的遞送途徑來有效提高劑量）。每天可根據需要使用多次劑量，以達到一種或多種INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的適當全身性水平或局部水平並達到INHBE蛋白活性的適當降低。

【0217】在又一些實施方案中，本發明的方法包括使用遞送媒介物，諸如生物相容的微粒、奈米顆粒或適於植入接受者（例如受試者）體內的

植入物。根據該方法可使用的示例性生物溶蝕植入物描述於PCT公開號WO 95/24929（以引用方式併入本文），該文獻描述了用於包含生物大分子的生物相容的且可生物降解的聚合物基質。

【0218】 不可生物降解的聚合物基質和可生物降解的聚合物基質均可用於本發明的方法中以將一種或多種INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑遞送至受試者。在一些實施方案中，基質可以是可生物降解的。基質聚合物可以是天然的或合成的聚合物。可基於期望釋放的時間段來選擇聚合物，通常為幾小時至一年或更長時間。通常，可使用在幾小時到三個月至十二個月範圍內的釋放時間。聚合物任選地呈水凝膠的形式，其可吸收高達其重量約90%的水，並且進一步任選地與多價離子或其他聚合物交聯。

【0219】 一般來講，在本發明的一些實施方案中，INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑可使用生物溶蝕植入物通過擴散方式或通過聚合物基質的降解進行遞送。用於此類用途的示例性合成聚合物是本領域熟知的。可生物降解的聚合物和不可生物降解的聚合物可用於使用本領域已知的方法遞送INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑。生物黏附聚合物諸如生物溶蝕水凝膠（參見H. S. Sawhney、C. P. Pathak和J. A. Hubell in Macromolecules, 1993, 26, 581-587，該文獻的教導內容以引用方式併入本文）還可用於遞送INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑以用於治療INHBE相關疾病或病症。另外的合適的遞送系統可包括時間釋放、延遲釋放或持續釋放遞送系統。此類系統可避免重複施用INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑，從而增加了對受試者和醫療保健

專業人員的便利性。許多類型的釋放遞送系統是可用的並且是本領域普通技術人員已知的。（參見例如美國專利號5,075,109、4,452,775、4,675,189、5,736,152、3,854,480、5,133,974和5,407,686（這些文獻中的每一篇的教導內容以引用方式併入本文））。此外，可使用基於泵的硬件遞送系統，其中一些泵適於植入。

【0220】 使用長期持續釋放植入物可能適合用於受試者和處於發展復發性INHBE相關疾病或病症的風險中的受試者的預防性治療。如本文所用，長期釋放意指植入物被構建和安排成遞送治療水平的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑至少長達10天、20天、30天、60天、90天、六個月、一年或更長時間。長期持續釋放植入物是本領域普通技術人員熟知的，包括上述一些釋放系統。

【0221】 INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的呈凍乾製劑或水性溶液的形式的治療性製劑可通過以下方式製備以用於儲存：將具有期望純度的分子或化合物與任選的藥學上可接受的載劑、賦形劑或穩定劑混合[“雷氏藥學大全（Remington's Pharmaceutical Sciences）”，第21版，（2006年）]。可接受的載劑、賦形劑或穩定劑在所採用的劑量和濃度下對接受者無毒，包括緩衝劑，諸如磷酸鹽、檸檬酸鹽和其他有機酸；抗氧化劑，包括抗壞血酸和甲硫氨酸；防腐劑（諸如十八烷基二甲基苄基氯化銨、氯化六甲雙銨、苯紮氯銨、苄索氯銨、苯酚、丁醇或苄醇、烷基對羥基苯甲酸酯（諸如甲基或丙基對羥基苯甲酸酯）、鄰苯二酚、間苯二酚、環己醇、3-戊醇和間甲酚）；低分子量（少於約10個殘基）多肽；蛋白，諸如血清白蛋白、明膠或免疫球蛋白；親水性聚合物，諸如聚乙烯吡咯烷酮；

氨基酸，諸如甘氨酸、穀氨醯胺、天冬醯胺、組氨酸、精氨酸或賴氨酸；單糖、二糖和其他碳水化合物，包括葡萄糖、甘露糖或糊精；螯合劑，諸如EDTA；糖類，諸如蔗糖、甘露糖醇、海藻糖或山梨糖醇；成鹽抗衡離子，諸如鈉；金屬絡合物（例如，Zn-蛋白絡合物）；和/或非離子型表面活性劑，諸如TWEEN®、PLURONICS®或聚乙二醇（PEG）。

細胞、受試者和對照

【0222】 本發明的方法可與細胞、組織、器官和/或受試者聯合使用。在本發明的一些方面，受試者是人或脊椎動物哺乳動物，包括但不限於狗、貓、馬、牛、山羊、小鼠、大鼠和靈長類動物，例如猴。因此，本發明可用於治療人和非人受試者的INHBE相關疾病或病症。在本發明的一些方面，受試者可以是農場動物、動物園動物、馴養動物或非馴養動物，並且本發明的方法可用於獸醫預防和治療方案。在本發明的一些實施方案中，受試者是人，並且本發明的方法可用於人預防和治療方案。

【0223】 可應用本發明的受試者的非限制性示例是被診斷患有、懷疑患有或處於患有與高於期望的INHBE表達和/或活性（也稱為“INHBE表達水平升高”）相關的疾病或病症的風險的受試者。與高於期望水平的INHBE表達和/或活性相關的疾病和病症的非限制性示例描述於本文別處。可將本發明的方法應用於在治療時已被診斷為患有與高於期望的INHBE表達和/或活性相關的疾病或病症的受試者，或被認為處於患有或發展與高於期望的INHBE表達和/或活性相關的疾病或病症的風險中的受試者。在本發明的一些方面，與高於期望的INHBE表達和/或活性水平相關的疾病或病症是急

性疾病或病症，並且在本發明的某些方面，與高於期望的INHBE表達和/或活性水平相關的疾病或病症是慢性疾病或病症。

【0224】 在一個非限制性示例中，將本發明的INHBE dsRNA藥劑施用於被診斷患有、懷疑患有或處於患有抑制素抵抗高膽固醇血症風險的受試者，該高膽固醇血症是其中期望降低INHBE表達的疾病。可將本發明的方法應用於在治療時已被診斷為患有該疾病或病症的受試者，或被認為處於患有或發展該疾病或病症的風險中的受試者。

【0225】 在另一個非限制性示例中，將本發明的INHBE dsRNA藥劑施用於被診斷患有2型糖尿病的受試者，該糖尿病是其中期望降低INHBE表達的疾病。可將本發明的方法應用於在治療時已被診斷為患有該疾病或病症的受試者，或被認為處於患有或發展該疾病或病症的風險中的受試者。

【0226】 可應用本發明的方法的細胞包括體外細胞、體內細胞、離體細胞。細胞可位於受試者體內、培養物中和/或懸浮液中，或者處於任何其他合適的狀態或條件下。可應用本發明的方法細胞可以是肝臟細胞、肝細胞、心臟細胞、胰腺細胞、心血管細胞、腎臟細胞或其他類型的脊椎動物細胞，包括人和非人哺乳動物細胞。在本發明的某些方面，可應用本發明的方法的細胞是未被確認為疾病細胞的健康正常細胞。在本發明的某些實施方案中，將應用本發明的方法和組合物的細胞應用於肝臟細胞、肝細胞、心臟細胞、胰腺細胞、心血管細胞、CNS細胞和/或腎臟細胞。在本發明的某些方面，對照細胞是正常細胞，但應當理解，患有疾病或病症的細胞在特定情況下也可用作對照細胞，例如用於比較患有疾病或病症的接受治療的細胞與患有該疾病或病症的未治療細胞的結果等。

【0227】根據本發明的方法，可測定INHBE多肽活性的水平並與INHBE多肽活性的對照水平進行比較。對照可以是預先確定的值，其可採取多種形式。它可以是單個截止值，諸如中值或平均值。它可基於比較組來建立，諸如在具有正常水平的INHBE多肽和/或INHBE多肽活性的組中和具有增加水平的INHBE多肽和/或INHBE多肽活性的組中。比較組的另一個非限制性示例可以是具有INHBE相關疾病或病症的一種或多種症狀或診斷的組；不具有該疾病或病症的一種或多種症狀或診斷的組；已經施用本發明的siRNA治療的受試者組；未施用本發明的siRNA治療的受試者組。通常，對照可基於處於適當年齡段的看起來健康的正常個體或看起來健康的細胞。應當理解，除了預先確定的值之外，根據本發明的對照還可以是與實驗材料同步測試的材料樣本。示例包括來自對照群體的樣本或通過製造產生的用於與實驗樣本同步測試的對照樣本。在本發明的一些實施方案中，對照可包括未接觸或未用本發明的INHBE dsRNA藥劑治療的細胞或受試者，並且在此類情況下，可將INHBE多肽和/或INHBE多肽活性的對照水平與接觸本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑的細胞或受試者中的INHBE多肽和/或INHBE多肽活性的水平進行比較。

【0228】在本發明的一些實施方案中，針對受試者測定的INHBE多肽水平可以是對照水平，將同一受試者在不同時間測定的INHBE多肽水平與之進行比較。在一個非限制性示例中，測定從未施用本發明的INHBE治療的受試者獲得的生物樣本中的INHBE水平。在一些實施方案中，該生物樣本是血清樣本。從受試者獲得的樣本中測定的INHBE多肽水平可用作受試者的基線或對照值。在本發明的治療方法中，在向受試者施用一次或多

次INHBE dsRNA藥劑後，可從受試者獲得一個或多個另外的血清樣本，並且可將後續一個或多個樣本中的INHBE多肽水平與受試者的對照/基線水平進行比較。此類比較可用於評估受試者的INHBE相關疾病或病症的發作、進展或消退。例如，從受試者獲得的基線樣本中的INHBE多肽水平高於在向受試者施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑後從同一受試者獲得的水平，這表明INHBE相關疾病或病症的消退，並且表明所施用的本發明的INHBE dsRNA藥劑對治療INHBE相關疾病或病症的功效。

【0229】 在本發明的一些方面，針對受試者測定的INHBE多肽水平和/或INHBE多肽活性水平中的一者或多者的值可用作對照值，以用於對該同一受試者中的INHBE多肽水平和/或INHBE活性水平的後續比較，從而允許評估相對於受試者中的“基線”INHBE多肽活性的變化。因此，初始INHBE多肽水平和/或初始INHBE多肽活性水平可存在於受試者中和/或針對該受試者進行測定，並且本發明的方法和化合物可用於降低該受試者中的INHBE多肽水平和/或INHBE多肽活性水平，其中該初始水平用作該受試者的對照水平。

【0230】 使用本發明的方法，可將本發明的INHBE dsRNA藥劑和/或INHBE反義多核苷酸藥劑施用於受試者。當與在先前時間點從受試者獲得的血清樣本中的INHBE多肽的施用前水平相比，或與非接觸對照水平（例如對照血清樣本中的INHBE多肽水平）相比，從受試者獲得的血清樣本中的INHBE多肽水平降低至少0.5%、1%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、95%或更多時，可評估本發明施用和治療的功效。

應當理解，INHBE多肽水平和INHBE多肽活性水平兩者均與INHBE基因表達水平相關。本發明的方法的某些實施方案包括將本發明的INHBE dsRNA和/或INHBE反義藥劑以有效抑制INHBE基因表達的量施用於受試者，從而降低該受試者中的INHBE多肽水平和INHBE多肽活性水平。

【0231】 本發明的一些實施方案包括測定從一個或多個受試者獲得的一個或多個生物樣本中的INHBE多肽的存在、不存在和/或量（本文也稱為水平）。該測定結果可用於評估本發明的治療方法的功效。例如，本發明的方法和組合物可用於測定從先前已施用本發明的INHBE dsRNA藥劑和/或INHBE反義藥劑治療的受試者獲得的生物樣本中的INHBE多肽水平。與針對受試者測定的INHBE多肽的預處理水平相比，或與非接觸對照生物樣本水平相比，從接受治療的受試者獲得的血清樣本中測定的INHBE多肽水平降低至少0.5%、1%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、95%或更多，這表明施用於受試者的治療的功效水平。

【0232】 在本發明的一些實施方案中，針對受試者測定的INHBE相關疾病或病症的生理特徵可以是對照測定結果，將同一受試者在不同時間的生理特徵測定結果與之比較。在一個非限制性示例中，生理特徵諸如INHBE表達的降低也可通過測量INHBE生物活性的降低，例如，或與INHBE水平升高（優選在血液、血清中）相關的其他病理來進行間接評估。在一個非限制性示例中，生理特徵諸如受試者的根據體重指數調整的腰臀比或LDL水平。

【0233】 從受試者獲得的樣本中測定的INHBE mRNA水平（和/或INHBE疾病或病症的其他生理特徵）可用作受試者的基線或對照值。在本

發明的治療方法中，在向受試者施用一次或多次INHBE dsRNA藥劑後，可從受試者獲得一個或多個另外的血清樣本，並將後續一個或多個樣本中的INHBE mRNA水平和/或INHBE蛋白水平分別與受試者的對照/基線水平和/或比率進行比較。此類比較可用於評估受試者的INHBE相關疾病或病症的發作、進展或消退。例如，從受試者獲得的基線樣本中的INHBE mRNA水平高於在向受試者施用本發明的INHBE dsRNA藥劑或INHBE反義多核苷酸藥劑後從同一受試者獲得的樣本中測定的INHBE mRNA水平，這表明INHBE相關疾病或病症的消退，並且表明施用本發明的INHBE dsRNA藥劑對治療INHBE相關疾病或病症的功效。

【0234】 在本發明的一些方面，針對受試者測定的INHBE相關疾病或病症的生理特徵中的一者或多者的值可用作對照值，以用於對該同一受試者中的生理特徵的後續比較，從而允許評估相對於受試者中的“基線”生理特徵的變化。因此，初始生理特徵可存在於受試者中和/或針對該受試者進行測定，並且本發明的方法和化合物可用於降低該受試者中的INHBE多肽水平和/或INHBE多肽活性水平，其中該初始生理特徵測定結果用作該受試者的對照。

【0235】 使用本發明的方法，可將本發明的INHBE dsRNA藥劑和/或INHBE反義多核苷酸藥劑以有效量施用於受試者，以用於治療INHBE疾病或病症。本發明的施用和治療功效可通過測定INHBE疾病或病症的一種或多種生理特徵的變化進行評估。在一個非限制性示例中，與在先前時間點從受試者獲得的血清樣本中的施用前脂質相比，或與非接觸對照水平（例如對照血清樣本中的INHBE mRNA水平）相比，從受試者獲得的血清樣本

中的INHBE mRNA水平降低至少0.5%、1%、5%、10%、20%、30%、40%、50%、60%、70%、80%、90%、95%或更多。應當理解受試者中的INHBE mRNA水平、INHBE蛋白水平，或脂質水平。本發明的方法的某些實施方案包括將本發明的INHBE dsRNA和/或INHBE反義藥劑以有效抑制INHBE基因表達的量施用於受試者，從而降低該受試者中的INHBE mRNA水平、INHBE蛋白水平，或者以其他方式積極影響該受試者的INHBE相關疾病或病症的生理特徵。

【0236】 本發明的一些實施方案包括使用諸如但不限於以下項的方法來測定INHBE相關疾病或病症的生理特徵的存在、不存在和/或變化：(1)評估從一個或多個受試者獲得的一個或多個生物樣本的生理特徵；(2)對受試者進行成像（例如但不限於獲得肝臟圖像）；和/或(3)對受試者進行身體檢查。該測定結果可用於評估本發明的治療方法的功效。

試劑盒

【0237】 還在本發明的範圍內的是包含一種或多種INHBE dsRNA藥劑和/或INHBE反義多核苷酸藥劑及其在本發明方法中的使用說明書的試劑盒。本發明的試劑盒可包含可用於治療INHBE相關疾病或病症的INHBE dsRNA藥劑、INHBE有義多核苷酸和INHBE反義多核苷酸藥劑中的一者或多者。可製備含有一種或多種INHBE dsRNA藥劑、INHBE有義多核苷酸和INHBE反義多核苷酸藥劑的試劑盒，以用於本發明的治療方法。本發明的試劑盒的組分可以水性介質或凍乾形式進行包裝。本發明的試劑盒可包含被區室化的載劑，以在其中封閉地容納一個或多個容器裝置或一系列容器

裝置，諸如試管、小瓶、燒瓶、瓶子、注射器等。第一容器裝置或第一系列容器裝置可容納一種或多種化合物，諸如INHBE dsRNA藥劑和/或INHBE有義或反義多核苷酸藥劑。第二容器裝置或第二系列容器裝置可容納靶向劑、標記劑、遞送劑等，它們可作為INHBE dsRNA藥劑和/或INHBE反義多核苷酸的一部分被包括在內以在本發明的治療方法的實施方案中施用。

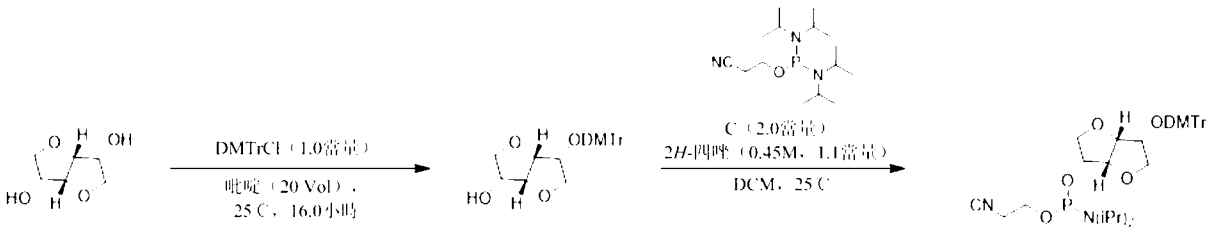
【0238】 本發明的試劑盒還可包含說明書。說明書通常為書面形式，並且將為實施試劑盒所包含的治療和基於該治療做出的決定提供指導。

【0239】 所提供的以下實施例用於說明本發明實踐的具體實例，並非旨在對本發明的範圍進行限制。對於本領域普通技術人員來說將顯而易見的是，本發明將應用於各種組合物和方法中。

實施例

【0240】 實施例1.

【0241】 亞磷醯胺化合物2（異甘露醇殘基（imann）亞磷醯胺）：



【0242】 將DMTrCl（232g，684mmol，1.0當量）的吡啶（400mL）溶液添加到異甘露醇化合物**A**（100g，684mmol，1.0當量）的吡啶（600mL）溶液中，並將混合物在25℃下攪拌12小時。LC-MS顯示化合物**A**完全消耗並檢測到一個具有期望質量的主峰。將所得反應混合物用水（500mL）稀

釋，用DCM（500mL×2）萃取，並將合併的有機相用鹽水（500mL）洗滌，經Na_2SO_4乾燥並真空濃縮，得到殘餘物。將殘餘物通過柱色譜（DCM/MeOH=100/1至50/1，0.1% Et_3N）純化，得到化合物**B**（150g，48.9%產率），為黃色固體。

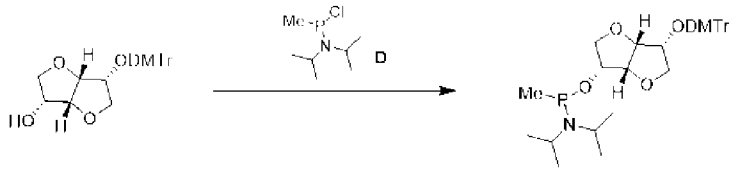
【0243】 ^{1}H NMR: EC4783-404-P1B1_C (400 MHz, DMSO-d_6) δ ppm 7.46 (br d, *J*=7.63 Hz, 2 H) 7.28 - 7.37 (m, 6 H) 7.19 - 7.25 (m, 1 H) 6.90 (br d, *J*=7.88 Hz, 4 H) 4.70 (d, *J*=6.50 Hz, 1 H) 3.99 - 4.09 (m, 6 H) 3.88 - 3.96 (m, 2 H) 3.83 (br dd, *J*=7.82, 6.94 Hz, 1 H) 3.74 (s, 6 H) 3.41 (br t, *J*=8.13 Hz, 1 H) 3.05 (t, *J*=8.44 Hz, 1 H) 2.85 (br t, *J*=7.50 Hz, 1 H)。

【0244】 在25℃和N_2氣氛下，向化合物**B**（80.0g，178mmol，1.0當量）的DCM（800mL）溶液中滴加2*H*-四唑（0.45M，436mL，1.1當量），然後向該混合物中滴加化合物**C**（80.6g，267mmol，85.0mL，1.5當量）的DCM（200mL）溶液。將反應混合物在25℃下攪拌1.0小時。LC-MS顯示化合物**B**完全消耗並檢測到一個具有期望質量的主峰。將所得反應混合物冷卻至-20℃並倒入冰冷的飽和$NaHCO_3$（500mL）中，用DCM（500mL×3）萃取，將合併的有機層用飽和$NaHCO_3$/鹽水=1:1（300mL/300mL）洗滌，經Na_2SO_4乾燥並真空濃縮（35℃），得到殘餘物（100mL）。將殘餘物通過柱色譜（Al_2O_3，DCM/MeOH=100/1至50/1，0.1% Et_3N）純化，得到化合物2（77g，119mmol，66.5%產率），為白色固體。

【0245】 ^{1}H NMR: EC4783-423-P1B1_C (400 MHz, DMSO-d_6) δ ppm 7.22 (br d, J=7.50 Hz, 2 H) 7.05 - 7.14 (m, 6 H) 6.96 - 7.02 (m, 1 H)

6.67 (br dd, J=8.82, 1.81 Hz, 4 H) 3.95 - 4.07 (m, 2 H) 3.73 - 3.83 (m, 1 H) 3.62 - 3.72 (m, 2 H) 3.48 - 3.53 (m, 6 H) 3.27 - 3.37 (m, 3 H) 3.11 (s, 6 H) 2.82 (td, J=8.54, 2.31 Hz, 1 H) 2.47 - 2.63 (m, 3 H) 2.28 (br d, J=1.63 Hz, 3 H) 0.82 - 1.00 (m, 13 H)。

【0246】 亞磷醯胺化合物1：



B　　化合物1

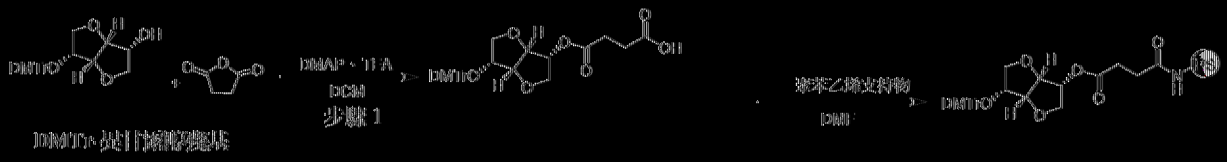
【0247】 在N_2氣氛和0℃至5℃下，向化合物**B**（500mg，1.11mmol，1.0當量）的DCM（5.0mL）溶液中添加化合物**D**（607mg，3.34mmol，3.0當量）和DIEA（432mg，3.34mmol，582μL，3.0當量），將混合物在25℃下攪拌1.0小時。LC-MS顯示化合物**B**完全消耗，LC-MS上顯示幾個新的峰示並檢測到約70.9%的期望化合物。將所得反應混合物冷卻至-20℃並倒入冷（0℃至5℃）的飽和$NaHCO_3$（5.0mL）溶液中，用DCM（5.0mL×2）萃取，將合併的有機層用冷（0℃至5℃）的飽和$NaHCO_3$/鹽水=1:1（5.0mL/5.0mL）洗滌，經Na_2SO_4乾燥並真空濃縮，得到殘餘物（約5mL）。將殘餘物通過柱色譜（鹼性Al_2O_3，石油醚/乙酸乙酯=10/1至5/1，0.1% Et_3N）純化，得到化合物**1**（280mg，471μmol，42.3%產率），為白色固體。

【0248】 ^{1}H NMR: EC10615-49-P1N (400 MHz, DMSO-d_6) δ ppm 7.44 (br d, *J*=7.63 Hz, 2 H), 7.31 (br t, *J*=7.94 Hz, 6 H), 7.18 - 7.26 (m, 1 H), 6.89 (brd, *J*=8.00 Hz, 4 H), 4.08 - 4.13 (m, 1 H), 3.95 - 4.03 (m, 1 H),

3.84 – 3.93 (m, 1 H), 3.77 – 3.83 (m, 1 H), 3.74 (s, 6 H), 3.43 – 3.53 (m, 3 H), 3.38 (br d, *J* 6.75 Hz, 1 H), 2.94 – 3.04 (m, 1 H), 2.70 – 2.85 (m, 1 H), 1.09 – 1.15 (m, 12 H), 1.07 (br s, 3 H)。

〔0249〕 其他亞磷醯胺可根據本文和/或現有技術所述的方法（諸如但不限於US426,220和WO02/36743）進行製備。

〔0250〕 實施例2.包含本發明的亞磷醯胺單體的固體支持物的製備



DMTr=雙(4-甲氧基苯基)苯基

(S)表示胺甲基聚乙烯大孔樹脂載劑部分

〔0251〕 在氮氣保護下，將二氯甲烷（19.50kg）添加到50L玻璃釜中並開始攪拌。將溫度控制在20℃至30℃，並將DMTr異甘露醇殘基（1.47kg）、三乙胺（1.50kg）、4-二甲基氨基吡啶（0.164kg）和琥珀酸酐（1.34kg）添加到該玻璃釜中。將體系在20℃至30℃下保持18小時，取樣並結束反應。將飽和碳酸氫鈉溶液（22.50kg）添加到反應體系中，攪拌10分鐘至20分鐘並使其分層。將有機相分離並將水相用二氯甲烷萃取兩次，將有機相合併，並經無水硫酸鈉乾燥，過濾並真空濃縮，得到殘餘物，形成1.83kg灰色至灰白色的固體。

〔0252〕 將N,N-二甲基甲醯胺（23.50kg）添加到100L玻璃釜中並攪拌。將溫度控制在20℃至30℃。在氮氣保護下，將上一步驟產物O-苯並三唑四甲基脲六氟磷酸鹽（0.33kg）和N,N-二異丙基乙胺（0.13kg）通過固體進料漏斗添加到上述100L玻璃釜中並攪拌10分鐘至30分鐘，然後倒入50L鋅桶中備用。將大孔胺甲基樹脂（3.25kg）（購自天津南開和成科學技

術有限公司，批號為HA2X1209，負荷容量為0.48mmol/g）通過固體進料漏斗添加到上述100L固相合成反應器中，將溫度控制在20℃至30℃，將N,N-二甲基甲醯胺（21.00kg+21.00kg）和上一步驟的鋅桶中的反應溶液添加到該固相合成反應器中。該體系進行保溫反應，並對固體負荷跟蹤至≥250μmol/g，並且負荷檢測方法為紫外光（UV）。在氮氣壓力下過濾該體系，將濾餅用N,N-二甲基甲醯胺洗滌三次（26.00kg+26.10kg+26.00kg），並將濾餅留在該釜中。將CAP.A（50%乙腈和50%乙酸酐，4.40kg+4.42kg+4.30kg）和CAP.B（20%吡啶和30% N-甲基咪唑和50%乙腈，4.40kg+4.40kg+4.47kg）添加到80L玻璃釜中，並在使用前攪拌3分鐘至8分鐘。重複該操作三次以加帽，並將乙腈（18.00kg+18.00kg+18.00kg+17.50kg+17.50kg）添加到固相合成釜中。在氮氣鼓泡達10分鐘至30分鐘後進行壓濾。重複該操作四次，在固相合成釜中將濾餅用氮氣吹掃2小時至4小時，然後轉移到50L壓濾罐中。將溫度控制在15℃至30℃，繼續乾燥，並在乾燥後得到黃色至白色固體產物，重量：3.516kg。

【0253】 可通過本領域技術人員熟知的方法，諸如反向無鹼基殘基（invab）方法，使用imann亞磷醯胺將異甘露醇殘基添加到寡核苷酸鏈的5'-端或3'-端，並進一步添加到該基團的靶標上。

【0254】 實施例3.INHBE RNAi藥劑的合成。

【0255】 根據以下通用方法合成上文表2至表3所示的INHBE RNAi藥劑雙鏈體：

【0256】 使用基於亞磷醯胺化學的成熟的固相合成方法，在寡核苷酸

合成儀上合成siRNA的有義鏈序列和反義鏈序列。寡核苷酸鏈的增長通過4步循環實現：脫保護、縮合、加帽以及用於添加每個核苷酸的氧化或硫化步驟。合成是在由可控孔徑玻璃（CPG，1000Å）製成的固體支持物上進行。單體亞磷醯胺可購自商業來源，或者可以是實施例1至實施例2，和/或WO2023/045995和/或WO2016/028649中的亞磷醯胺化合物。本文中的磷醯亞胺化合物可作為單體亞磷醯胺與3'-端連接，並且進一步與CPG固體支持物連接。在連接在5'-端處的情況下，亞磷醯胺化合物可用於最終的偶聯反應，並且可進一步與靶配體綴合（如果需要）。

【0257】 具有GalNAc配體簇的亞磷醯胺（GLS-5*或GLS-15*亞磷醯胺作為非限制性示例）公開於WO2023/045995A1中（該文獻全文併入本文）。對於用於體外篩選的siRNA（表2），以2μmol的規模進行合成，並且對於用於體內測試的siRNA（表3），以5μmol或更大的規模進行合成。在GalNAc配體（GLO-n亞磷醯胺作為非限制性示例公開於WO2023/045995A1中（該文獻全文併入本文））連接在有義鏈的3'-端處的情況下，使用連接GalNAc配體的CPG固體支持物。在GalNAc配體（GLS-5*或GLS-15*作為非限制性示例連接在有義鏈的5'-端，具有GalNAc配體簇的GLS-5*或GLS-15*亞磷醯胺公開於WO2023/045995A1中（該文獻全文併入本文））連接在有義鏈的5'-端處的情況下，將GalNAc亞磷醯胺用於最後的偶聯反應。

【0258】 有義鏈和反義鏈是通過具有4步循環的固相合成來合成的，其詳述如下：用3%三氯乙酸（TCA）的二氯甲烷溶液對4,4'-二甲氧基三苯甲基保護基團（DMT）進行脫保護。5-乙硫基-1H-四唑用作活化劑。I_2的

THF/Py/H_2O溶液和苯乙醯基二硫化物（PADS）的吡啶/MeCN溶液分別用於氧化反應和硫化反應。在最終的固相合成步驟之後，裂解結合固體支持物的低聚物，並通過用40重量%甲胺的水溶液和28%氫氧化銨溶液的1:1體積溶液處理來除去保護基團。為了合成用於體外篩選的siRNA，將粗混合物濃縮。將其餘固體溶解在1.0M NaOAc中，並添加冰冷的EtOH以沉澱出單鏈產物，為鈉鹽，其無需進一步純化即可用於退火。為了合成用於體內測試的siRNA，將單鏈粗產物通過離子配對反相HPLC（IP-RP-HPLC）進一步純化。通過溶解在1.0M NaOAc中並通過添加冰冷的EtOH沉澱進行沉澱，將來自IP-RP-HPLC的純化單鏈寡核苷酸產物轉化為鈉鹽。將等摩爾互補的有義鏈和反義鏈寡核苷酸在水中退火，形成雙鏈siRNA產物，將其凍乾，得到蓬鬆的白色固體。

【0259】 在某些研究中，用於將包含GalNAc（本文也稱為GalNAc遞送化合物）的靶向基團連接至有義鏈的5'-端的方法包括在固相合成的最後偶聯步驟中使用GalNAc亞磷醯胺（GLS-5*或GLS-15*亞磷醯胺），使用合成過程，諸如在進行寡核苷酸鏈的增長（即，將核苷酸添加到有義鏈的5'-端）時所使用的過程。

【0260】 在一些研究中，用於將包含GalNAc的靶向基團連接至有義鏈的3'-端的方法包括使用包括GLO-n的固體支持物（CPG）。在一些研究中，用於將包含GalNAc的靶向基團連接至有義鏈的3'-端的方法包括通過酯鍵將GalNAc靶向基團連接至CPG固體支持物，並且在合成有義鏈時使用所得的具有所連接的GalNAc靶向基團的CPG，這導致該GalNAc靶向基團連接在有義鏈的3'-端處。

【0261】 可通過本領域技術人員熟知的方法，諸如反向無鹼基殘基（invab）方法，將異甘露醇殘基添加到寡核苷酸鏈的5'端或3'端，並且/或進一步添加到該GalNAc靶向基團的靶標上。

【0262】 實施例4.INHBE siRNA雙鏈體的體外篩選

【0263】 將Huh7細胞用胰蛋白酶消化並調節至合適的密度，與INHBE-psiCHECK(TM)-2和Lipofectamine 2000（Invitrogen-11668-019）的複合物混合並接種到96孔板中。根據製造商建議的方案，進行接種的同時，使用Lipofectamine RNAiMax（Invitrogen -13778-150）將測試siRNA或對照siRNA轉染到細胞中。將兩種濃度（1nM和10nM）的siRNA重複測試三次。

【0264】 第1天，INHBE-psiCHECK(TM)-2轉染（一塊板）

【0265】 (1)將2.5μg INHBE-psiCHECK(TM)-2載體質粒轉移到不含核糖核酸酶的離心管（溶液混合物#1）中。

【0266】 (2)在一個燒瓶中添加胰蛋白酶以分離Huh7細胞，並使用Vi-Cell計數儀對細胞進行計數，將細胞密度調整至1×10^5/ml。

【0267】 (3)將7.5μL Lipofectamine 2000（Invitrogen-11668-019）轉移到溶液混合物#1管中，進行混合。

【0268】 (4)將步驟3中的溶液添加到細胞懸浮液中，進行混合，並將懸浮液分配到96孔板中（100μl/孔）。

【0269】 第2天，siRNA轉染

【0270】 (1)用Opti-MEM®培養基稀釋Lipofectamine®RNAiMAX試劑。

【0271】 (2)用不含RNA的水稀釋siRNA，以製備12×儲備液。

【0272】 (3)將等體積稀釋的RNAiMax和siRNA混合。將混合物在室溫下孵育15分鐘，形成複合物。

【0273】 (4)將45μl/孔的化合物Lipofectamine® RNAiMAX(Opti-MEM)混合物添加到225μl/孔的DMEM新鮮培養基中，並棄去測定板中的上清液，將120μl/孔的化合物混合物添加到96孔板中。

【0274】 (5)無化合物對照孔被定義為用INHBE-psiCHECK(TM)-2轉染且未用siRNA處理的細胞；空白對照是僅含細胞的孔。

【0275】 第3天，Dual-Glo®螢光素酶測定

【0276】 (1)將試劑添加到測定板中，等待10分鐘以使細胞發生裂解。

【0277】 (2)將100μl細胞裂解物轉移到板中，然後測量firefly發光。

【0278】 (3)將50μl Dual-Glo® Stop & Glo®試劑添加到測定板中並混合，等待10分鐘，然後測量Renilla發光。

【0279】 (4)計算相對表達

【0280】 數據分析

【0281】 樣本孔的比率=(樣本Renilla發光-背景空白)/(樣本Firefly發光-背景空白)

【0282】 無化合物對照孔的比率=(對照Renilla發光-背景空白)/(對照樣本Firefly發光-背景空白)

【0283】 抑制%=100-(樣本孔的比率/無化合物對照的平均比率)×100%

【0284】 所使用的雙鏈體序列對應於表5所示的那些。

【0285】 表5提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體外研究的實驗結果。所使用的雙鏈體序列對應於表2所示的序列。

雙鏈體AV#	平均抑制%（平均值±SD）	
	10nM	1nM
AV01591	28.52±6.21	NA
AV01592	69.13±4.05	40.74±1.64
AV01593	58.98±0.23	38.38±2.73
AV01594	11.53±0.94	15.07±3.35
AV01595	46.54±1.33	29.64±3.46
AV01596	10.17±1.86	10.20±1.87
AV01597	18.25±5.54	16.84±0.43
AV01598	20.05±4.13	NA
AV01599	28.62±2.66	15.65±5.27
AV01600	45.03±1.03	22.79±0.57
AV01602	19.48±9.21	17.75±5.58
AV01603	29.29±0.95	19.58±2.31
AV01604	56.58±1.59	35.39±0.89
AV01605	63.92±2.80	46.82±1.47
AV01606	58.71±3.35	22.56±2.12
AV01609	33.39±1.66	22.90±3.53
AV01610	25.01±4.76	16.65±0.98
AV01611	2.59±10.27	17.77±4.23
AV01613	18.13±5.71	-1.36±0.80
AV01618	18.02±1.01	11.82±3.29
AV01621	41.80±3.55	19.30±3.63
AV01622	24.64±3.25	NA
AV01623	35.57±1.81	16.19±0.66
AV01624	38.68±4.20	18.41±0.61
AV01625	12.97±5.16	NA
AV01626	-19.28±6.31	1.85±4.90
AV01627	-16.59±1.45	-0.62±5.53
AV01629	37.39±3.60	20.26±3.83
AV01630	12.78±3.88	NA
AV01631	-13.16±2.07	NA
AV01632	17.89±0.18	12.29±2.83
AV01633	15.28±3.96	NA
AV01634	30.36±3.62	0.17±2.45
AV01635	-1.48±1.97	NA
AV01636	25.04±1.36	NA
AV01637	-1.61±2.50	-0.70±3.53
AV01638	30.93±0.56	20.82±4.20
AV01639	NA	0.77±2.84
AV01641	0.03±1.46	NA
AV01644	27.59±0.61	10.54±0.95
AV01645	37.22±1.27	11.86±0.61
AV01646	-19.65±10.64	-1.14±3.77
AV01647	47.29±5.82	24.66±5.04

AV01648	-14.58±7.64	NA
AV01649	-13.32±3.14	NA
AV01650	43.88±1.54	16.35±9.38
AV01651	58.34±0.26	29.91±1.03
AV01652	22.03±3.44	NA
AV01653	-11.43±3.44	NA
AV01654	-10.44±13.39	NA
AV01656	31.58±2.69	NA
AV01658	48.94±0.41	11.60±3.27
AV01659	45.39±5.14	10.26±2.44
AV01660	37.65±0.45	16.93±2.47
AV01661	48.52±2.25	19.87±0.89
AV01662	29.82±1.48	NA
AV01663	27.17±3.29	0.11±5.46
AV01664	-2.82±2.30	NA
AV01665	-1.64±3.69	NA
AV01666	-10.27±3.88	NA
AV01667	50.78±3.06	24.22±9.55
AV01668	50.65±2.33	29.64±6.40
AV01670	15.75±0.75	-1.68±2.86
AV01671	15.09±0.39	NA
AV01672	47.36±3.28	22.11±8.49
AV01673	42.82±5.42	12.38±7.12
AV01674	56.91±5.15	26.33±2.95
AV01675	38.24±2.73	16.10±2.24
AV01676	36.84±9.20	NA
AV01677	27.22±4.20	-0.03±3.77
AV01678	NA	-1.46±6.48
AV01679	21.44±1.44	NA
AV01680	48.32±2.32	26.09±3.97
AV01681	45.52±2.63	22.99±1.98
AV01682	23.87±1.06	13.60±10.42
AV01683	-19.88±2.37	NA
AV01686	38.95±1.45	13.56±14.47
AV01687	38.48±0.83	19.08±2.42
AV01688	28.65±6.17	NA
AV01689	-15.58±5.04	NA
AV01691	-0.89±8.60	NA
AV01692	31.16±1.25	NA
AV01693	-14.87±11.87	NA
AV01694	37.81±1.92	12.09±3.32
AV01695	11.33±1.41	15.75±12.95
AV01697	27.29±3.21	NA
AV01698	45.00±0.67	14.15±1.51
AV01699	71.22±1.56	38.21±1.33
AV01700	60.56±0.86	30.35±1.97
AV01701	55.84±1.00	30.12±0.60
AV01702	35.72±1.50	25.21±7.34
AV01703	-13.71±9.41	NA

AV01704	18.98±3.17	NA
AV01705	63.04±0.55	30.13±1.73
AV01706	56.30±2.31	37.61±2.21
AV01707	75.35±1.04	44.23±0.86
AV01708	54.04±1.48	28.21±2.07
AV01709	44.63±0.51	26.44±1.22
AV01710	45.01±2.41	35.58±3.07

【0286】 實施例5 INHBE siRNA雙鏈體的體內測試

【0287】 在第1天，通過靜脈內施用編碼人INHBE和螢光素酶基因的腺相關病毒8（AAV8）載體的溶液來感染雌性C57BL/6J小鼠（每組3隻）。在第8天，向小鼠皮下施用單一的3mg/kg或10mg/kg的INHBE siRNA藥劑或PBS。通過比較siRNA處理前和處理後的血清樣本中螢光素酶活性的變化，計算化合物的RNAi活性，通過相同時期的對照組中螢光素酶活性的變化進行歸一化。結果示於表6至表8中。

【0288】 表6提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體內研究的實驗結果。所使用的雙鏈體序列對應於表3所示的序列。

雙鏈體AD#	相對於第8天的剩餘（平均值±SD）		劑量 mg/kg
	第15天	第22天	
AD00963	0.9±0.4	0.75±0.25	3
AD00965	0.96±0.11	0.78±0.31	3
AD00966	0.8±0.25	0.82±0.31	3
AD00967	0.97±0.4	1.24±0.28	3
AD00969	0.72±0.32	0.39±0.14	3
AD00970	0.55±0.21	0.7±0.33	3
AD00971	0.62±0.17	0.51±0.1	3
AD00972	0.76±0.34	0.49±0.03	3
AD00973	0.6±0.19	0.58±0.35	3
AD00974	0.57±0.25	0.48±0.13	3
AD00975	0.68±0.2	0.43±0.16	3
AD00980	0.53±0.22	0.68±0.26	3
AD00981	0.47±0.13	0.49±0.19	3
AD00982	0.41±0.23	0.33±0.05	3

AD00983	0.78±0.25	0.44±0.17	3
AD00985	0.7±0.42	0.54±0.15	3
AD00986	0.72±0.22	0.65±0.22	3
AD00987	0.99±0.97	0.52±0.13	3

【0289】 表7提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體內研究的實驗結果。所使用的雙鏈體序列對應於表3所示的序列。

雙鏈體AD#	相對於第8天的剩餘（平均值±SD）		劑量mg/kg
	第15天	第22天	
AD00964	0.69±0.25	0.54±0.2	3
AD00977	0.53±0.08	0.48±0.11	3
AD01272	0.56±0.16	0.48±0.07	3
AD01274	1.16±0.45	0.69±0.22	3
AD01275	0.71±0.06	0.67±0.21	3
AD01276	1.17±0.39	0.81±0.25	3
AD01277	0.85±0.29	0.89±0.16	3

【0290】 表8提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體內研究的實驗結果。所使用的雙鏈體序列對應於表3所示的序列。

雙鏈體AD#	相對於第8天的剩餘（平均值±SD）			劑量 mg/kg
	第15天	第22天	第29天	
AD00926	0.3±0.08	0.32±0.14	0.42±0.03	10
AD00927	0.27±0.12	0.26±0.08	0.42±0.11	10
AD00964	0.37±0.24	0.28±0.12	0.48±0.13	10
AD00968	0.4±0.12	0.43±0.11	0.48±0.18	10
AD00969	0.45±0.21	0.55±0.38	0.78±0.42	10
AD00970	0.45±0.2	0.48±0.12	0.75±0.64	10
AD00971	0.55±0.14	0.71±0.21	0.86±0.27	10
AD00972	0.39±0.12	0.4±0.12	0.61±0.22	10
AD00974	0.6±0.18	0.41±0.06	0.31±0.14	10
AD00975	0.58±0.07	0.96±0.3	1.1±0.25	10
AD00976	0.77±0.22	0.92±0.19	1.07±0.32	10
AD00977	0.38±0.07	0.4±0.15	0.62±0.19	10
AD00978	0.36±0.08	0.47±0.14	0.73±0.39	10
AD00979	0.49±0.27	0.4±0.38	0.64±0.71	10
AD00980	0.74±0.13	0.93±0.43	1.62±0.28	10

AD00981	0.28±0.08	0.37±0.07	0.75±0.2	10
AD00982	0.33±0.11	0.27±0.09	0.65±0.15	10
AD00984	0.23±0.17	0.5±0.37	0.79±0.71	10
AD01273	0.46±0.37	0.59±0.21	0.5±0.13	10
AD01274	0.22±0.07	0.52±0.12	0.66±0.57	10
AD01275	0.29±0.15	0.36±0.04	0.97±0.31	10
AD01276	0.36±0.1	0.59±0.32	1±0.43	10

【0291】 實施例6.INHBE siRNA雙鏈體的體外篩選

【0292】 將Huh7細胞用胰蛋白酶消化並調節至合適的密度，接種到96孔板中。接種第二天，按照製造商建議的方案，使用 Lipofectamine 2000 (Invitrogen-11668-019) 將 psiCHECK(TM)-2 載體質粒、空白載體 PCNDA3.0、siRNA 或對照 siRNA 複合物轉染細胞。以不同濃度（10 nM 和 1 nM）對 siRNA 進行三次重複測試。

【0293】 第1天，加入胰酶解離一瓶中的Huh7細胞，用Vi-Cell計數儀計數細胞，調整細胞密度為1*10^5/ml，用DMEM培養基培養。

【0294】 第 2 天，INHBE-psiCHECK(TM)-2 載體/空白載體 pCDNA3.0/siRNAs/Lipofectamine 2000 混合物轉染

【0295】 (1) 將適當的 Lipofectamine 2000 (Invitrogen-11668-019) 與 Opti-MEM® 培養基 (溶液混合物#1) 混合。最終每孔加入 0.3 µl Lipofectamine 2000 和 4.7 µl Opti-MEM® 培養基。

【0296】 (2) 將適當的 INHBE--psiCHECK(TM)-2 載體、空白 pCNDNA 3.0 載體和 siRNA 與 Opti-MEM® 培養基 (溶液混合物#2) 混合。

【0297】 (3) 將等體積的溶液混合物#1 和混合物#2 混合，最終每孔

加入 10 μl。將混合物在室溫下孵育 15 分鐘以形成複合物。

【0298】 (4) 去除DMEM培養基，加入10 μl混合溶液mix#1和mix#2，以及90 μl新鮮DMEM培養基。

【0299】 (5) 無化合物對照孔定義為用INHBE-psiCHECK(TM)-2載體和空白載體pCNDNA 3.0轉染且未經siRNA處理的細胞；空白對照為僅有細胞的孔。

【0300】 第3天，按照Dual Glo Luciferase Reporter Gene Assay Kit（YEASEN，11405ES80）的說明書進行Dual Glo Luciferase Assay

【0301】 表9 提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體外研究的實驗結果。所使用的雙鏈體序列對應於表2所示的序列。

雙鏈體 AV#	平均抑制%（平均值±SD）	
	10nM	1nM
AV05265	46.24±10.91	30.84±3.87
AV05266	-1.90±5.72	0.74±8.12
AV05267	34.62±2.18	26.11±5.93
AV05268	39.89±7.55	47.73±2.26
AV05269	73.27±2.72	76.52±1.75
AV05270	19.42±5.57	22.51±0.53
AV05271	11.40±7.01	12.90±8.08
AV05272	-15.27±3.64	16.40±17.24
AV05273	36.68±5.15	48.26±8.12
AV05274	38.98±2.03	31.32±4.31
AV05275	10.68±3.08	16.52±8.17
AV05276	65.28±1.31	44.39±9.75
AV05277	63.66±2.83	64.77±6.80
AV05278	36.31±2.44	26.87±9.97
AV05279	59.54±1.83	52.09±1.84
AV05280	1.90±3.87	-3.54±4.61
AV05281	-2.71±1.50	-24.41±8.25
AV05282	9.98±8.35	-7.71±7.64
AV05283	9.07±1.78	5.84±5.90
AV05284	25.93±2.89	18.47±4.49
AV05285	71.42±4.80	47.56±7.56
AV05286	45.35±3.50	31.45±0.40
AV05287	43.41±6.98	37.69±2.48
AV05288	24.20±4.14	14.34±5.65
AV05289	11.79±1.32	27.92±9.71
AV05290	8.12±2.05	5.44±2.29
AV05291	14.86±3.86	14.21±5.15

AV05292	57.28±3.47	50.16±5.23
AV05293	64.92±1.77	41.77±7.84
AV05294	47.97±1.27	21.50±11.75
AV05295	62.98±1.20	64.60±3.39
AV05296	35.23±1.15	28.97±5.91
AV05297	62.74±1.51	40.25±2.81
AV05298	12.06±5.54	14.02±2.78
AV05299	8.03±4.67	12.88±6.86
AV05300	18.43±8.69	12.66±4.06
AV05301	56.07±5.40	51.62±2.26
AV05302	61.81±4.42	47.43±3.05
AV05303	49.14±8.91	51.26±2.63
AV05304	47.70±5.54	44.81±4.88
AV05305	7.29±4.83	18.57±18.11
AV05306	5.18±5.88	7.59±4.94
AV05307	68.35±1.65	61.17±3.43
AV05308	80.04±0.70	70.79±3.77
AV05309	27.39±8.55	33.39±8.24
AV05310	77.83±1.15	79.63±3.52
AV05311	63.47±1.59	61.07±2.96
AV05312	61.69±0.34	60.48±4.77
AV05313	72.46±1.43	60.18±1.17
AV05314	69.56±1.74	50.30±4.19
AV05315	38.41±0.72	34.85±4.45
AV05316	76.64±2.02	64.93±1.15
AV03977	47.16±1.41	73.06±2.08
AV03979	14.83±11.10	33.78±3.25

【0302】 實施例7. INHBE siRNA雙鏈體的體外篩選

【0303】 將Huh7細胞用胰蛋白酶消化並調節至合適的密度，接種到96孔板中。接種第二天，按照製造商建議的方案，使用 Lipofectamine 2000 (Invitrogen-11668-019) 將 psiCHECK(TM)-2 載體質粒、空白載體 PCNDA3.0、siRNA 或對照 siRNA 複合物轉染細胞。以不同濃度（10 nM 和 1 nM）對 siRNA 進行三次重複測試。

【0304】 第1天，加入胰酶解離一瓶中的Huh7細胞，用Vi-Cell計數儀計數細胞，調整細胞密度為1*10^5/ml，用DMEM培養基培養。

【0305】 第 2 天，INHBE-psiCHECK(TM)-2 載體/空白載體 pCDNA3.0/siRNAs/Lipofectamine 2000 混合物轉染

【0306】 (1) 將適當的 Lipofectamine 2000 (Invitrogen-11668-019) 與 Opti-MEM® 培養基 (溶液混合物#1) 混合。最終每孔加入 0.3 μl Lipofectamine 2000 和 4.7 μl Opti-MEM® 培養基。

【0307】 (2) 將適當的 INHBE--psiCHECK(TM)-2 載體、空白 pCNDNA 3.0 載體和 siRNA 與 Opti-MEM® 培養基 (溶液混合物#2) 混合。

【0308】 (3) 將等體積的溶液混合物#1 和混合物#2 混合，最終每孔加入 10 μl。將混合物在室溫下孵育 15 分鐘以形成複合物。

【0309】 (4) 去除DMEM培養基，加入10 μl混合溶液mix#1和mix#2，以及90 μl新鮮DMEM培養基。

【0310】 (5) 無化合物對照孔定義為用INHBE-psiCHECK(TM)-2載體和空白載體pCNDNA 3.0轉染且未經siRNA處理的細胞；空白對照為僅有細胞的孔。

【0311】 第3天，按照Dual Glo Luciferase Reporter Gene Assay Kit（YEASEN，11405ES80）的說明書進行Dual Glo Luciferase Assay

【0312】 表10 提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體外研究的實驗結果。所使用的雙鏈體序列對應於表2所示的序列。

雙連體 AV#	平均抑制%（平均值±SD）	
	1nM	0.1nM
AV06796	42.37±1.91	-34.28±4.12
AV06797	52.43±1.37	-28.88±2.69
AV06798	28.43±3.46	-36.44±9.46
AV06799	-5.24±4.18	-16.38±8.52
AV06800	43.79±3.07	-4.08±4.28
AV06801	-3.74±2.22	-25.37±9.70
AV06802	-10.26±4.75	-20.27±3.86
AV06803	-15.92±5.38	-25.00±7.87
AV06804	-31.24±5.04	-43.66±6.89
AV06805	-40.70±2.81	-52.42±6.85

AV06806	-18.98±3.31	-38.02±9.15
AV06807	10.50±2.30	-22.65±7.82
AV06808	11.30±7.89	-21.01±6.10
AV06809	21.38±1.24	-17.23±0.52
AV06810	-0.07±7.11	-12.44±8.51
AV06811	17.01±2.89	-7.25±4.12
AV06812	-33.90±7.81	-53.16±11.08
AV06813	9.96±2.82	-27.84±6.20
AV06814	-7.11±3.56	-22.47±6.29
AV06815	10.43±4.39	-5.33±4.99
AV06816	8.63±3.18	-18.90±6.52
AV06817	9.05±2.39	-13.73±7.89
AV06818	22.01±2.47	-3.30±2.63
AV06819	7.89±4.87	-0.87±1.72
AV06820	-26.39±3.48	-42.44±7.51
AV06821	7.19±0.75	-34.73±6.32
AV06822	34.60±2.77	-5.92±1.93
AV06823	18.45±3.51	-10.91±3.78
AV06824	-9.55±5.49	-16.76±10.78
AV06825	-5.48±4.48	-20.50±3.41
AV06826	-3.28±1.64	-9.74±1.96
AV06827	11.55±1.19	5.81±4.46
AV06828	37.96±3.50	-25.30±4.45
AV06829	14.99±1.19	-20.90±3.34
AV06830	-9.02±8.02	-20.26±1.83
AV06831	0.28±5.88	-7.59±11.23
AV06832	0.95±1.81	-10.87±3.27
AV06833	21.38±3.72	0.10±6.14
AV06834	45.68±2.10	6.22±7.78
AV06835	12.71±5.09	6.65±4.04
AV06836	-26.32±3.91	-37.69±5.16
AV06837	-18.34±0.94	-23.44±3.30
AV06838	-11.63±3.24	-17.63±4.02
AV06839	-9.38±8.65	-20.68±7.04
AV06840	-4.19±3.65	-18.82±11.48
AV06841	46.84±0.79	5.10±3.86
AV06842	16.44±2.33	-0.74±1.93
AV06843	49.71±3.32	17.26±5.31
AV06844	-11.63±5.55	-38.27±5.72
AV06845	17.51±4.01	-14.12±9.01
AV06846	13.24±4.44	-2.14±8.72
AV06847	7.68±3.39	-1.24±6.60
AV06848	8.48±3.41	-1.84±1.70
AV06849	10.82±6.05	3.92±1.60
AV06850	7.21±1.52	-0.34±0.76
AV06851	26.21±1.69	6.63±3.55
AV06852	-30.30±3.98	-35.12±10.69
AV06853	-19.28±1.85	-23.76±7.56
AV06854	58.09±0.52	15.55±3.10
AV06855	73.07±1.21	30.05±5.86
AV06856	22.33±1.73	-1.43±5.61
AV06857	27.42±2.43	0.73±3.05
AV06858	10.03±4.68	-1.87±5.70
AV06859	35.02±2.50	-3.07±3.59

AV06860	-0.72±4.82	-25.46±2.58
AV06861	-3.44±3.13	-23.47±11.28
AV06862	35.38±2.20	1.71±4.33
AV06863	50.70±5.84	14.60±2.54
AV06864	53.58±2.58	14.40±0.89
AV06865	50.36±3.88	16.72±4.91
AV06866	41.94±4.28	11.74±3.01
AV06867	-2.04±3.62	-16.01±3.67
AV06868	-19.63±2.89	-22.28±2.45
AV06869	-1.56±2.99	-14.87±1.76
AV06870	8.08±4.31	-2.69±4.89
AV06871	5.28±2.33	-4.88±4.86
AV06872	7.17±4.28	-1.50±5.13
AV06873	58.88±1.51	15.34±2.46
AV06874	19.99±1.20	0.16±3.40
AV06875	65.31±0.45	11.74±3.32
AV06876	-25.31±0.94	-29.12±3.04
AV06877	8.81±2.60	-14.86±1.59
AV06878	-6.26±4.03	-1.70±2.57
AV06879	15.42±2.24	4.98±3.68
AV06880	5.36±5.90	8.63±2.33
AV06881	27.80±2.95	14.04±2.20
AV06882	8.09±1.03	7.64±1.62
AV06883	15.52±5.73	5.11±1.57
AV06884	-16.58±1.99	-20.86±6.17
AV06885	5.82±1.61	-19.57±6.98
AV06886	5.57±6.13	4.46±6.08
AV06887	10.66±5.00	2.15±5.32
AV06888	50.50±2.61	15.94±6.49
AV06890	15.07±0.35	1.05±7.98
AV06891	14.42±4.76	6.09±2.12

【0313】 表11 提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體外研究的實驗結果。所使用的雙鏈體序列對應於表2所示的序列。

雙連體 AV#	平均抑制%（平均值±SD）	
	1nM	0.1nM
AV06892	11.04±1.06	-8.57±7.05
AV06893	34.62±3.46	-1.03±3.33
AV06894	20.07±3.83	7.37±5.79
AV06895	6.46±12.23	9.67±1.12
AV06896	8.82±1.83	13.47±2.35
AV06897	21.82±2.37	15.36±3.72
AV06898	63.04±3.89	22.18±2.86
AV06899	1.90±1.57	-29.83±5.97
AV06900	8.94±4.86	2.39±5.91
AV06901	2.60±14.95	-0.18±5.21
AV06902	35.99±3.83	8.80±4.56
AV06903	11.34±3.62	8.03±4.19
AV06904	39.22±3.59	15.32±6.07
AV06905	50.86±0.53	17.85±5.31

AV06906	30.20±3.55	2.87±5.79
AV06907	27.87±4.10	-4.56±3.49
AV06908	1.64±5.09	-20.29±7.66
AV06910	16.88±1.80	-9.06±2.97
AV06911	36.77±2.27	6.42±3.05
AV06912	22.68±2.45	4.88±2.84
AV06913	39.25±3.86	7.56±2.08
AV06914	12.26±5.59	7.38±3.02
AV06915	0.02±1.27	-4.20±1.35
AV06916	-6.41±4.77	-11.00±4.90
AV06917	-16.85±3.52	-10.55±7.53
AV06918	-8.15±5.45	-6.09±5.58
AV06919	-1.17±10.81	6.42±3.93
AV06920	65.03±2.78	26.36±6.75
AV06921	14.20±4.84	3.39±2.80
AV06922	27.59±2.84	7.55±3.29
AV06923	18.53±1.38	16.99±5.55
AV06924	-20.84±3.99	-33.88±3.98
AV06925	24.78±3.27	-12.72±2.38
AV06926	48.13±2.33	1.59±3.58
AV06927	76.95±1.53	32.16±0.60
AV06928	55.18±2.38	13.52±5.21
AV06929	21.32±7.88	5.41±8.14
AV06930	27.74±8.05	10.87±5.99
AV06931	17.16±4.23	5.99±1.84
AV06932	-24.88±3.37	-34.38±3.91
AV06933	45.58±4.13	-14.64±10.03
AV06934	73.55±0.37	19.69±6.74
AV06935	38.62±2.65	1.24±10.91
AV06936	20.31±1.45	-1.93±5.70
AV06937	0.16±6.63	-1.69±5.43
AV06938	28.24±5.77	2.45±1.72
AV06939	25.73±1.21	16.93±4.46
AV06940	-1.99±7.77	-22.97±2.82
AV06941	-0.23±6.19	-7.62±3.72
AV06942	-2.04±5.06	6.22±6.04
AV06943	17.86±3.84	9.25±5.65
AV06944	31.38±3.77	10.50±1.51
AV06945	42.43±4.06	18.15±1.77
AV06946	48.62±1.86	13.61±4.68
AV06947	9.12±6.09	11.99±3.02
AV06948	-28.04±4.22	-33.55±6.02
AV06949	3.87±8.56	-19.64±1.26
AV06950	21.33±4.86	-1.89±5.22
AV06951	36.22±2.86	1.34±8.75
AV06952	11.03±4.01	3.64±5.00
AV06953	37.74±3.52	11.69±3.58
AV06954	11.16±1.45	0.75±7.41
AV06955	1.57±0.35	-29.79±7.42
AV06956	-7.67±4.02	-29.18±4.28
AV06957	8.33±3.64	-8.54±2.90
AV06958	40.69±4.12	2.41±1.91
AV06959	49.29±4.46	17.00±2.81
AV06960	17.40±5.56	14.97±1.87

AV06961	49.30±3.31	17.98±1.18
AV06962	66.03±2.30	26.97±1.98
AV06963	-9.69±8.95	-16.76±5.92
AV06964	39.86±1.32	-22.81±3.88
AV06965	-4.50±6.17	-30.21±10.79
AV06966	6.02±3.20	-11.22±7.54
AV06967	57.07±1.57	6.07±9.42
AV06968	71.15±4.33	25.93±11.57
AV06969	59.83±2.90	14.23±1.84
AV06970	65.08±1.07	24.38±4.33
AV06971	60.62±1.19	9.91±4.97
AV06972	49.46±0.82	-19.31±5.79
AV06973	51.63±2.26	4.76±2.34
AV06974	18.33±2.25	2.84±5.90
AV06975	73.20±0.28	23.68±4.72
AV06976	49.38±2.59	16.91±5.67
AV06977	33.10±3.84	9.63±4.38
AV06978	24.58±3.15	9.52±7.09
AV06979	32.59±4.44	11.67±9.70
AV06980	-37.68±3.03	-37.65±7.19
AV06981	39.10±3.47	-10.21±8.70
AV06982	44.43±4.18	-1.01±8.69
AV06983	9.74±1.24	-9.09±5.44
AV06984	26.22±2.04	2.01±6.94
AV06985	35.07±4.63	-2.13±9.19
AV06986	43.28±2.36	2.67±6.72
AV06987	58.23±1.02	14.71±6.44

【0314】 表12 提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體外研究的實驗結果。所使用的雙鏈體序列對應於表2所示的序列。

雙連體 AV#	平均抑制%（平均值±SD）	
	1nM	0.1nM
AV06988	66.91±0.97	12.54±5.09
AV06989	5.80±1.48	-0.80±4.14
AV06990	38.03±2.94	6.47±5.20
AV06991	26.73±2.40	8.71±1.28
AV06992	67.73±1.03	23.10±5.03
AV06993	61.61±0.96	19.88±2.18
AV06995	-13.90±5.61	-31.65
AV06996	23.64±1.73	-7.61±13.44
AV06997	42.46±3.17	-0.35±2.60
AV06998	45.91±2.55	13.62±6.52
AV06999	23.98±2.67	9.67±5.17
AV07000	72.65±0.29	24.34±4.13
AV07001	22.99±3.56	11.74±6.63
AV07002	47.58±1.63	17.12±4.10
AV07003	-0.67±5.54	-23.46
AV07004	-15.04±4.31	-11.78±3.14
AV07005	36.87±0.38	-5.52±2.27
AV07006	62.05±1.51	7.70±1.82

AV07007	63.22±0.84	14.97±4.48
AV07008	15.82±3.46	7.39±2.61
AV07009	58.16±3.46	12.49±5.74
AV07010	36.69±4.58	7.92±6.32
AV07011	1.54±4.62	-12.40
AV07012	67.00±0.51	10.01±1.48
AV07013	1.03±7.56	-10.20±7.38
AV07014	73.89±0.78	30.59±8.57
AV07016	64.04±2.58	10.36±8.57
AV07017	31.89±0.72	2.36±7.34
AV07018	14.50±3.47	-5.04±1.75
AV07019	31.93±7.62	-2.21
AV07020	-17.44±3.09	-20.99±3.24
AV07021	-7.81±2.12	-10.62±4.87
AV07022	-3.00±2.38	-2.40±4.24
AV07023	46.47±1.46	12.67±4.10
AV07025	14.81±2.03	10.41±4.96
AV07026	25.70±0.87	8.83±3.18
AV07027	17.35±3.08	-3.96
AV07028	49.33±5.73	3.96±2.90
AV07029	15.91±3.38	-13.89±9.09
AV07030	46.78±3.52	6.65±0.73
AV07031	81.67±0.63	50.83±4.78
AV07032	12.56±3.07	0.64±8.18
AV07033	14.31±4.68	4.69±4.44
AV07034	12.49±6.47	4.09±4.01
AV07035	7.48±2.93	-9.31
AV07036	-27.05±3.27	-32.72±3.09
AV07037	-6.48±5.59	-12.68±4.00
AV07038	1.38±2.33	-0.70±3.53
AV07039	16.17±2.50	-3.77±2.01
AV07040	19.38±3.24	-8.65±7.39
AV07041	36.06±1.66	2.36±5.97
AV07042	48.24±0.38	-1.19±6.74
AV07043	28.55±0.76	-1.25
AV07044	-5.43±1.94	-31.65±3.20

【0315】 表13 提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體外研究的實驗結果。所使用的雙鏈體序列對應於表2所示的序列。

雙連體 AV#	平均抑制%（平均值±SD）	
	1nM	0.1nM
AV06889	33.91±3.33	-2.24±5.74
AV06909	12.90±7.26	-14.12±3.90
AV06994	-8.65±4.02	-9.03±3.66
AV07015	43.82±1.99	4.57±7.03
AV07024	3.98±3.55	1.09±14.10
AV01591	25.44±7.64	2.48±9.45
AV01592	68.93±3.93	30.02±4.50

【0316】 實施例8 INHBE siRNA雙鏈體的體內測試

【0317】 在第1天，通過靜脈內施用編碼人INHBE和螢光素酶基因的腺相關病毒8（AAV8）載體的溶液來感染雌性C57BL/6J小鼠（每組3隻）。在第8天，向小鼠皮下施用單一的10mg/kg的INHBE siRNA藥劑或鹽水。通過比較siRNA處理前和處理後的血清樣本中螢光素酶活性的變化，計算化合物的RNAi活性，通過相同時期的對照組中螢光素酶活性的變化進行歸一化。結果示於表14至表15中。

【0318】 表14提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體內研究的實驗結果。所使用的雙鏈體序列對應於表3所示的序列。

雙連體 AD#	相對於第 8 天的螢光素酶剩餘（平均值±SD）		Dose(mg/kg)
	Day22	Day29	
Saline	1±0.44	1±0.32	/
AD01588	0.69±0.09	0.69±0.12	10
AD02406	0.55±0.04	1.01±0.23	10
AD02407	0.76±0.08	2.04±0.47	10
AD02408	1.16±0.16	1.52±0.26	10
AD02409	0.84±0.18	0.71±0.22	10
AD02410	1.05±0.32	0.85±0.13	10
AD02411	0.34±0.09	0.72±0.15	10
AD02412	0.35±0.07	0.55±0.09	10
AD02413	1.04±0.37	0.71±0.14	10
AD02414	1.09±0.47	1.91±1.08	10
AD02415	0.06±0.02	0.03±0.01	10
AD02416	0.34±0.07	0.4±0.05	10
AD02417	0.22±0.02	0.38±0.08	10
AD02418	0.32±0.07	0.55±0.11	10
AD02419	0.52±0.16	1.01±0.2	10
AD02420	0.31±0.06	0.72±0.13	10
AD02421	0.83±0.17	1.61±0.36	10
AD02422	0.13±0.02	0.36±0.06	10
AD02423	0.49±0.13	0.94±0.12	10
AD02424	0.19±0.04	0.38±0.12	10
AD02425	0.33±0.09	0.82±0.2	10
AD02426	0.62±0.32	0.73±0.19	10
AD02427	0.42±0.07	0.73±0.1	10
AD02428	0.23±0.04	0.32±0.11	10

【0319】 表15提供了使用各種INHBE RNAi藥劑抑制INHBE表達的體內研究的實驗結果。所使用的雙鏈體序列對應於表3所示的序列。

雙連體 AD#	相對於第 8 天的螢光素酶剩餘（平均值±SD）	Dose(mg/kg)
	Day22	
Saline	1±0.32	/
AD01588	0.56±0.19	10
AD03238	0.48±0.05	10
AD03239	0.36±0.08	10
AD03240	0.66±0.16	10
AD03241	0.42±0.12	10
AD03242	0.67±0.04	10
AD03243	0.46±0.1	10
AD03244	0.53±0.07	10
AD03245	0.34±0.07	10
AD03246	0.44±0.03	10
AD03247	0.25±0.09	10
AD03248	0.34±0.07	10
AD03249	0.47±0.06	10
AD03250	0.39±0.07	10
AD03252	0.59±0.08	10
AD03255	0.96±0.18	10
AD03256	0.47±0.04	10
AD03257	0.76±0.08	10
AD03258	0.59±0.08	10
AD03259	0.89±0.18	10
AD03260	1.24±0.29	10
AD03263	0.48±0.11	10
AD03264	0.37±0.05	10

【0320】 等同物

【0321】 儘管本文已經描述並示出了本發明的若干實施方案，但是本領域普通技術人員將容易地設想用於執行本文所述的功能和/或獲得本文所述的結果和/或一個或多個優點的各種其他裝置和/或結構，並且此類變化和/或修改中的每一者均被認為在本發明的範圍內。更一般地，本領域技術人員將容易地理解，本文所述的所有參數、尺寸、材料和構型都是示例性的，並且實際的參數、尺寸、材料和/或構型將取決於使用本發明的教導

內容的一個或多個具體應用。本領域技術人員將認識到或能夠僅使用常規實驗來確定本文描述的本發明的具體實施方案的許多等同物。因此，應當理解，前述實施方案僅以舉例的方式呈現，並且在所附申請專利範圍及其等同物的範圍內；本發明可以不同於具體描述和要求保護的方式來實踐。本發明涉及本文所述的每個單獨的特徵、系統、製品、材料和/或方法。此外，如果此類特徵、系統、製品、材料和/或方法不是相互矛盾的，則兩個或更多個此類特徵、系統、製品、材料和/或方法的任何組合均包括在本發明的範圍內。

【0322】 如本文所定義和使用的所有定義應當理解為受控於字典的定義、以引用方式併入的文獻中的定義和/或所定義術語的普通含義。

【0323】 除非明確地相反指明，否則如本說明書和申請專利範圍中所使用的不定冠詞“一”和“一個”應當理解為意指“至少一個”。

【0324】 如本說明書和申請專利範圍中所使用的短語“和/或”應當理解為意指如此結合的要素：即，在一些情況下聯合存在並且在其他情況下分離存在的要素中的“任一者或兩者”。除了由“和/或”從句明確標識的元件之外，還可任選地存在其他要素，無論與明確標識的那些要素是否相關，除非清楚地指出相反情況。

【0325】 本申請中引用或提及的所有參考文獻、專利和專利申請以及出版物均以引用方式全文併入本文。

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【發明申請專利範圍】

【請求項1】 一種用於抑制INHBE的表達的雙鏈核糖核酸（dsRNA）藥劑，其中所述dsRNA藥劑包含有義鏈和反義鏈，其中所述有義鏈包含與SEQ ID NO: 1、3、5或7的核苷酸序列相差不超過3個核苷酸的至少15個連續核苷酸，並且所述反義鏈包含與SEQ ID NO: 2、4、6或8的核苷酸序列相差不超過3個核苷酸的至少15個連續核苷酸，其中所述有義鏈和所述反義鏈彼此能夠部分地、基本上或完全互補，並且任選地包含靶向配體。

【請求項2】 如請求項1所述的dsRNA藥劑，其中所述dsRNA藥劑包含有義鏈和反義鏈，其中所述有義鏈包含與SEQ ID NO: 1的核苷酸351-381、361-391、398-428、520-550、521-551、554-584、576-606、619-649、625-655、627-657、628-658、629-659、631-661、632-662、633-663、639-669、742-772、761-791、763-793、766-796、768-798、769-799、775-805、776-806、777-807、778-808、779-809、780-810、783-813、785-815、817-847、875-905、876-906、883-913、884-914、950-980、951-981、974-1004、975-1005、981-1011、982-1012、1032-1062、1035-1065、1092-1122、1093-1123、1094-1124、1095-1125、1102-1132、1116-1146、1126-1156、1127-1157、1141-1171、1196-1226、1197-1227、1198-1228、1200-1230、1207-1237、1208-1238、1209-1239、1213-1243、1215-1245、1230-1260、1237-1267、1265-1295、1278-1308、1296-1326、1298-1328、1299-1329、1302-1332、1304-1334、1305-1335、1308-1338、1344-1374、1381-1411、1382-1412、1383-1413、1389-1419、1390-1420、1391-1421、1393-1423、1399-1429、1424-1454、1425-1455、1426-1456、1427-

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【請求項3】 如請求項2所述的dsRNA藥劑，其中所述有義鏈包含與SEQ ID NO: 1的核苷酸354-378、364-388、401-425、523-547、524-548、557-581、579-603、622-646、628-652、630-654、631-655、632-656、634-658、635-659、636-660、642-666、745-769、764-788、766-790、769-793、771-795、772-796、778-802、779-803、780-804、781-805、782-806、783-807、786-810、788-812、820-844、878-902、879-903、886-910、887-911、953-977、954-978、977-1001、978-1002、984-1008、985-1009、1035-1059、1038-1062、1095-1119、1096-1120、1097-1121、1098-1122、1105-1129、1119-1143、1129-1153、1130-1154、1144-1168、1199-1223、1200-1224、1201-1225、1203-1227、1210-1234、1211-1235、1212-1236、1216-1240、1218-1242、1233-1257、1240-1264、1268-1292、

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【請求項4】 如請求項1所述的dsRNA藥劑，其中所述反義鏈包含與INHBE RNA轉錄本互補的區域，所述區域包含與表1至表3中的任一個表中列出的反義序列中的任一者相差不超過1、2、或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸。

【請求項5】 如請求項1所述的dsRNA藥劑，其中所述反義鏈包含與INHBE RNA轉錄本互補的區域，所述區域包含來自表1至表3中的任一個表中列出的反義序列中的任一者的至少15、16、17、18、19、20或21個連續核苷酸。

【請求項6】 如請求項1至5中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含有義鏈和反義鏈，所述反義鏈中的核苷酸位置2至18包含與INHBE RNA轉錄本互補的區域，所述區域具有與表1至表3中的一個表中列出的反義序列之一相差0、1、2或3個核苷酸的至少15、16、17、18、19、20或21個連續核苷酸，並且任選地包含靶向配體。

【請求項7】 如請求項1至6中任一項所述的dsRNA藥劑，其中與INHBE RNA轉錄本互補的所述區域包含與表1至表3中的一個表中列出的

反義序列之一相差不超過3個核苷酸的至少15、16、17、18、或19個連續核苷酸。

【請求項8】 如請求項1至7中任一項所述的dsRNA藥劑，其中所述dsRNA的反義鏈與SEQ ID NO: 1的任一靶區域基本上或完全互補，並且優選地所述dsRNA藥劑包含表1至表3中的任一個表中示出的反義鏈序列。

【請求項9】 如請求項1至8中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑中的有義鏈序列與反義鏈序列至少基本上互補或完全互補，優選地，其中所述dsRNA藥劑包含表1至表3中的任一個表中示出的有義鏈序列。

【請求項10】 如請求項1至9中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含表1至表3中的任一個表中作為雙鏈體序列示出的序列。

【請求項11】 如請求項1至10中任一項所述的dsRNA，其中所述dsRNA藥劑包含至少一個經修飾的核苷酸。

【請求項12】 如請求項1至11中任一項所述的dsRNA藥劑，其中所述有義鏈和/或所述反義鏈中的所有或基本上所有核苷酸都是經修飾的核苷酸。

【請求項13】 如請求項1至12中任一項所述的dsRNA藥劑，其中所述有義鏈與所述反義鏈互補，其中所述反義鏈包含與INHBE RNA轉錄本的一部分互補的區域，其中每條鏈的長度為約15至約30個核苷酸，其中所述有義鏈包含能夠由式(I)表示的序列：

$$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3' \quad (I)；$$

其中：

每個N'_F表示經2'-氟修飾的核苷酸；每個N'_{N1}和N'_{N2}獨立地表示經修飾或未修飾的核苷酸；每個N'_L獨立地表示經修飾或未修飾的核苷酸但不表示經2'-氟修飾的核苷酸，並且m'和n'各自獨立地為0至7的整數。

【請求項14】 如請求項1至12中任一項所述的dsRNA藥劑，其中所述有義鏈與所述反義鏈互補，其中所述反義鏈包含與INHBE RNA轉錄本的一部分互補的區域，其中每條鏈的長度為約18至約30個核苷酸，其中所述反義鏈包含可以由式(II)表示的序列：

$$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_{M4}\ N_{M5}\ N_L\ N_L\ N_{M6}\ N_L\ N_{M7}\ N_L\ N_L\ N_F\ N_Z\text{-}5' \quad (II)$$

；

其中：

每個N_F表示經2'-氟修飾的核苷酸；每個N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}和N_{M7}獨立地表示經修飾或未修飾的核苷酸；每個N_L和/或N_Z獨立地表示經修飾或未修飾的核苷酸但不表示經2'-氟修飾的核苷酸，並且n為0至7的整數。

【請求項15】 如請求項1至12中任一項所述的dsRNA藥劑，其中所述有義鏈與所述反義鏈互補，其中所述反義鏈包含與INHBE RNA轉錄本互補的區域，其中所述互補區域包含至少15個連續核苷酸，其中所述dsRNA包括由式(III)表示的雙鏈體：

有義鏈：$5'\text{-}(N'_L)_{n'}N'_L\ N'_L\ N'_L\ N'_L\ N'_F\ N'_L\ N'_F\ N'_L\ N'_{N1}\ N'_{N2}\ N'_L\ N'_L\ N'_L\ N'_L\ N'_L\ (N'_L)_{m'}\text{-}3'$

反義鏈：$3'\text{-}(N_L)_n\ N_{M1}\ N_L\ N_{M2}\ N_L\ N_F\ N_L\ N_{M3}\ N_{M4}N_{M5},\ N_L\ N_L\ N_{M6}\ N_L\ N_{M7}$

$N_L N_L N_F N_Z$-5′

(III)；

其中：

每條鏈的長度為約18至約30個核苷酸；

每個N_F和N'_F獨立地表示經2'-氟修飾的核苷酸；N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}、N_{M7}、N'_{N1}和N'_{N2}各自獨立地表示經修飾或未修飾的核苷酸；N'_{N1}和N'_{N2}包括僅一個經2'-氟修飾的核苷酸；N_{M1}、N_{M2}、N_{M3}、N_{M4}、N_{M5}、N_{M6}和N_{M7}具有僅三個經2'-氟修飾的核苷酸；每個N_Z、N_L和N'_L獨立地表示經修飾或未修飾的核苷酸但不表示經2'-氟修飾的核苷酸，並且m′、n′和n各自獨立地為0至7的整數。

【請求項16】 如請求項1至15中任一項所述的dsRNA藥劑，其中所述一個或多個經修飾的核苷酸獨立地選自：2'-O-甲基核苷酸、2'-氟核苷酸、2'-脫氧核苷酸、2'3'-開環核苷酸模擬物、鎖核苷酸、非鎖核酸核苷酸（UNA）、乙二醇核酸核苷酸（GNA）、2'-F-阿拉伯糖核苷酸、2'-甲氧基乙基核苷酸、無鹼基核苷酸、核糖醇、反向核苷酸、反向無鹼基核苷酸、異甘露醇核苷酸、反向2'-Ome核苷酸、反向2'-脫氧核苷酸、經2'-氨基修飾的核苷酸、經2'-烷基修飾的核苷酸、嗎啉基核苷酸、3'-OMe核苷酸、包含5'-硫代磷酸酯基團的核苷酸、包含磷酸酯模擬物的核苷酸、與膽甾醇基衍生物或十二烷酸雙癸醯胺基團連接的末端核苷酸、經2'-氨基修飾的核苷酸、包含氨基磷酸酯或非天然鹼基的核苷酸。

【請求項17】 如請求項1至16中任一項所述的dsRNA藥劑，所述dsRNA藥劑包含在所述反義鏈的5′-端處的E-乙烯基膦酸酯核苷酸。

【請求項18】 如請求項1至17中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含至少一個硫代磷酸酯核苷間鍵。

【請求項19】 如請求項1至17中任一項所述的dsRNA藥劑，其中所述有義鏈包含至少一個硫代磷酸酯核苷間鍵。

【請求項20】 如請求項1至17中任一項所述的dsRNA藥劑，其中所述反義鏈包含至少一個硫代磷酸酯核苷間鍵。

【請求項21】 如請求項1至17中任一項所述的dsRNA藥劑，其中所述有義鏈包含1、2、3、4、5或6個硫代磷酸酯核苷間鍵。

【請求項22】 如請求項1至17中任一項所述的dsRNA藥劑，其中所述反義鏈包含1、2、3、4、5或6個硫代磷酸酯核苷間鍵。

【請求項23】 如請求項1至22中任一項所述的dsRNA藥劑，其中所述經修飾的有義鏈是表2至表3中的一個表中示出的經修飾的有義鏈序列。

【請求項24】 如請求項1至22中任一項所述的dsRNA藥劑，其中所述經修飾的反義鏈是表2至表3中的一個表中示出的經修飾的反義鏈序列。

【請求項25】 如請求項1至24中任一項所述的dsRNA藥劑，其中所述有義鏈與所述反義鏈互補或基本上互補，並且所述互補區域的長度為16至23個核苷酸。

【請求項26】 如請求項1至25中任一項所述的dsRNA藥劑，其中所述互補區域的長度為19至21個核苷酸。

【請求項27】 如請求項1至26中任一項所述的dsRNA藥劑，其中每條鏈的長度不超過30個核苷酸。

【請求項28】 如請求項1至26中任一項所述的dsRNA藥劑，其中每條鏈

的長度不超過25個核苷酸。

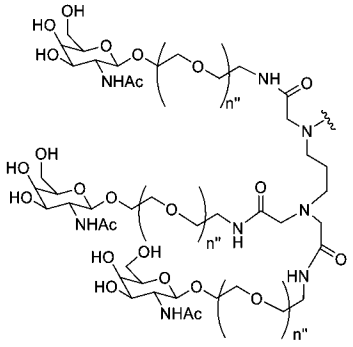
【請求項29】 如請求項1至26中任一項所述的dsRNA藥劑，其中每條鏈的長度不超過23個核苷酸。

【請求項30】 如請求項1至29中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含至少一個經修飾的核苷酸並且還包含一個或多個靶向基團或連接基團。

【請求項31】 如請求項30所述的dsRNA藥劑，其中所述一個或多個靶向基團或連接基團與所述有義鏈綴合。

【請求項32】 如請求項30或31所述的dsRNA藥劑，其中所述靶向基團或連接基團包括N-乙醯基-半乳糖胺（GalNAc）。

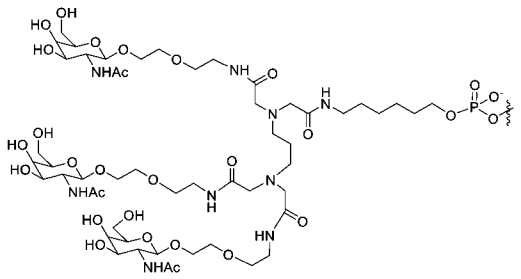
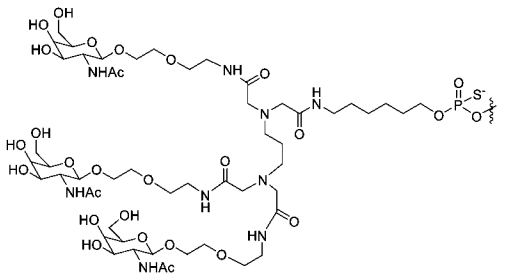
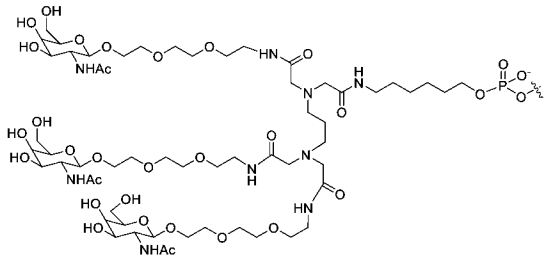
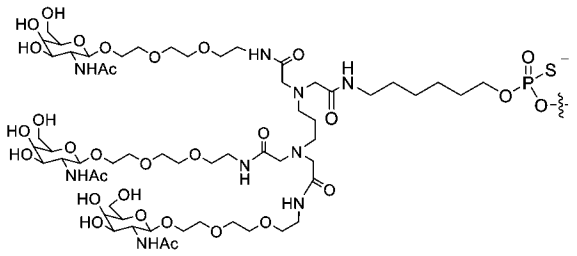
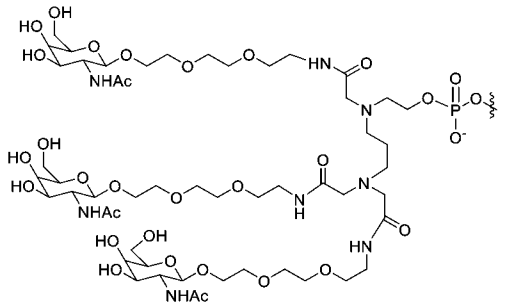
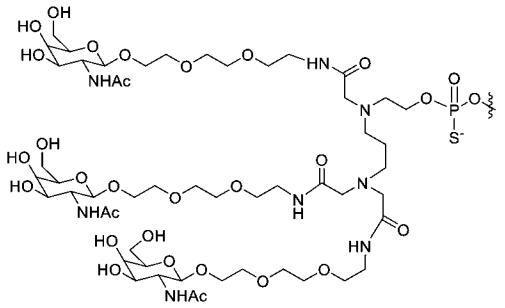
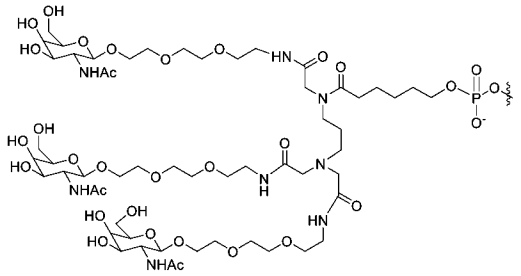
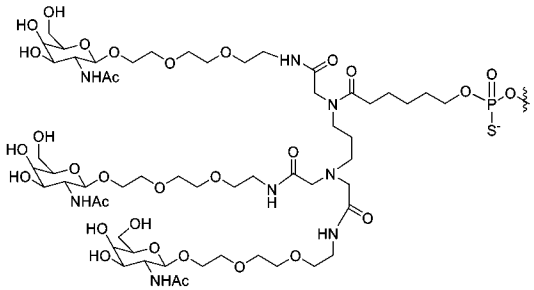
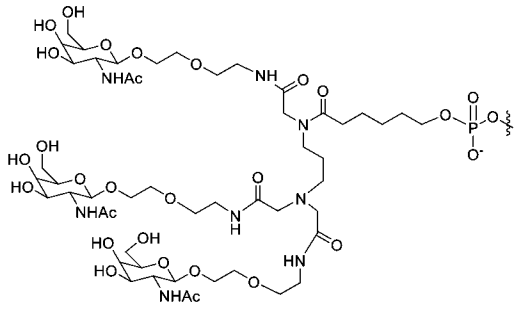
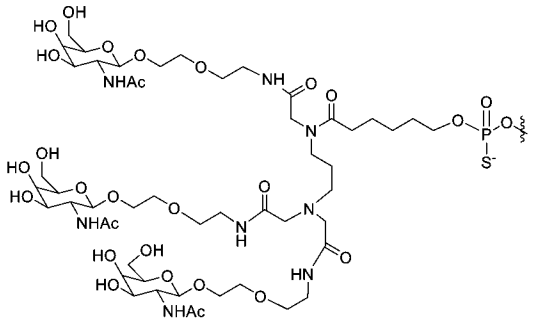
【請求項33】 如請求項30至32中任一項所述的dsRNA藥劑，其中所述靶向基團具有以下結構：

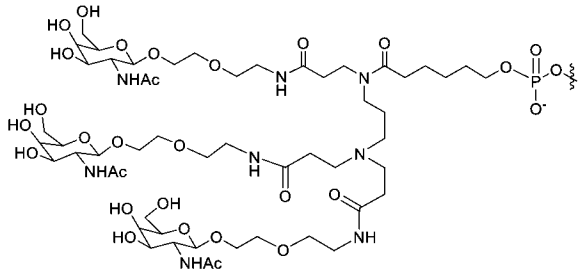
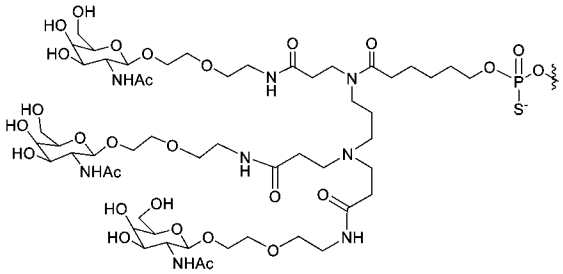
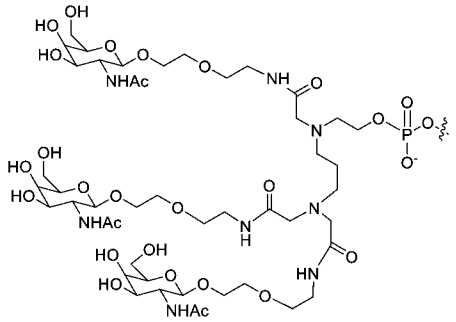
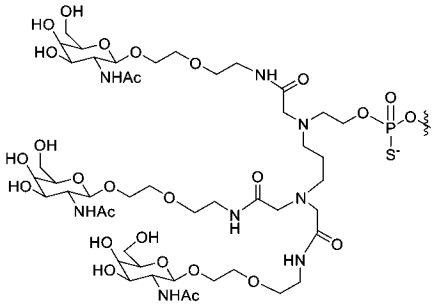
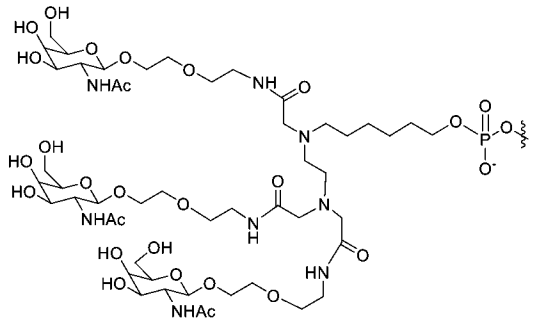
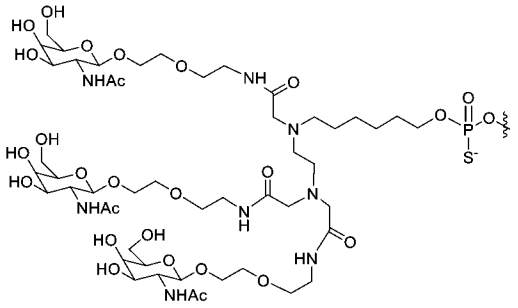
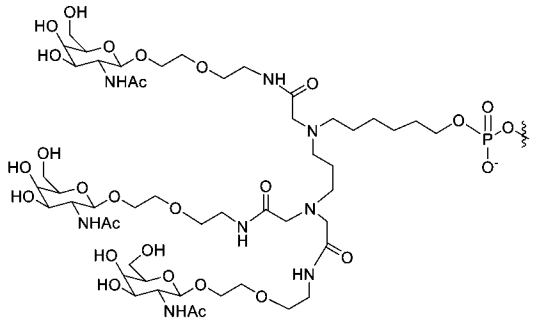
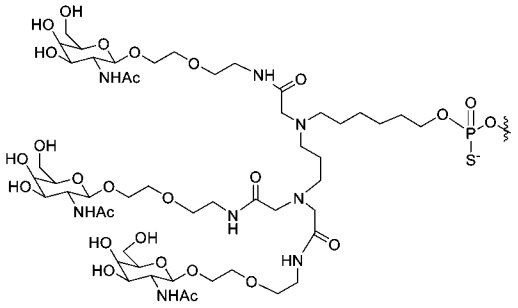
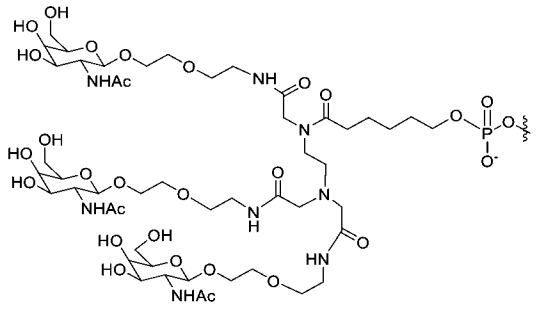
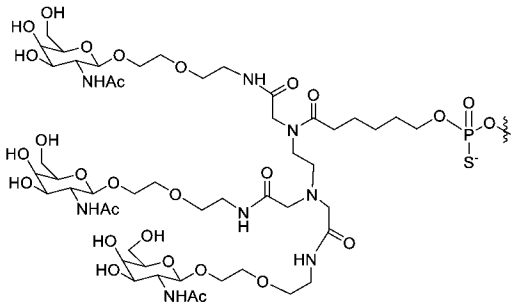


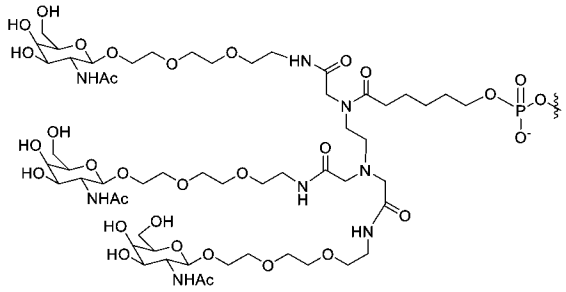
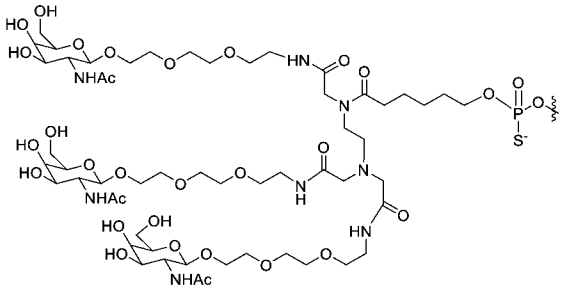
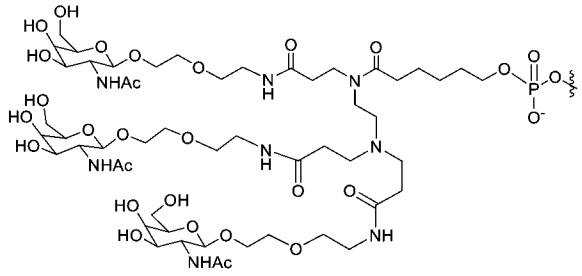
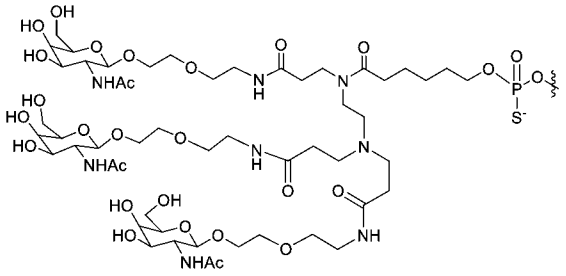
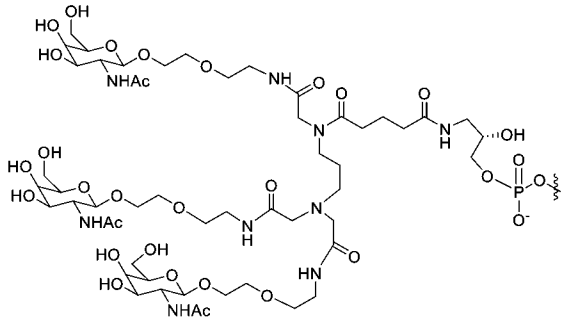
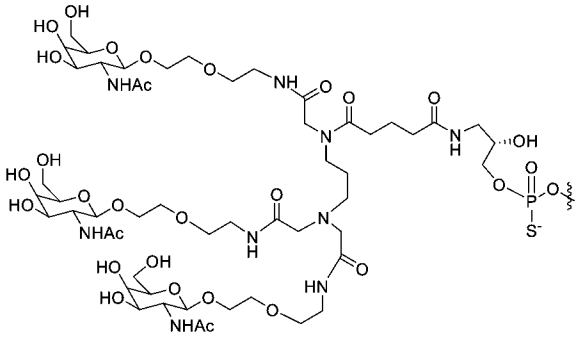
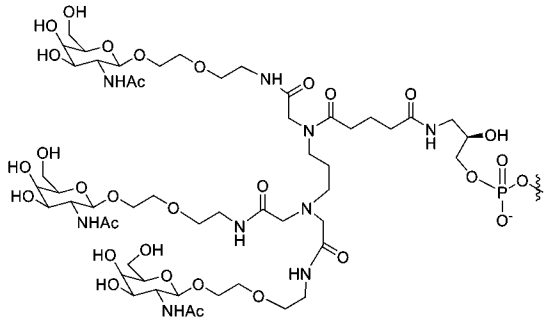
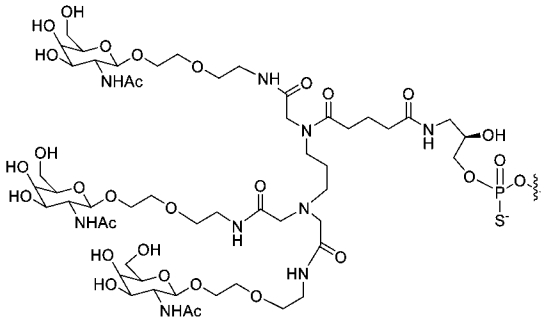
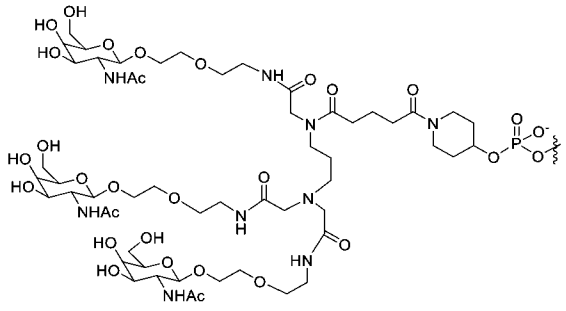
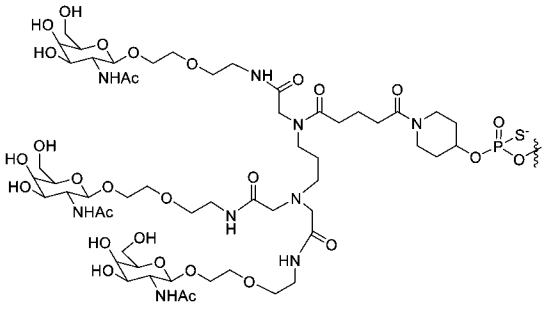
；

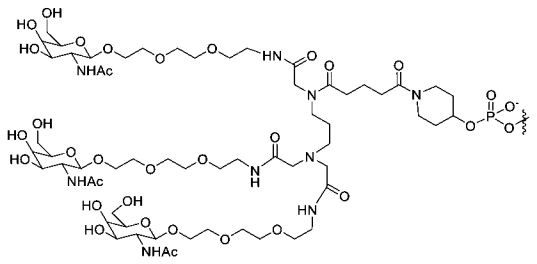
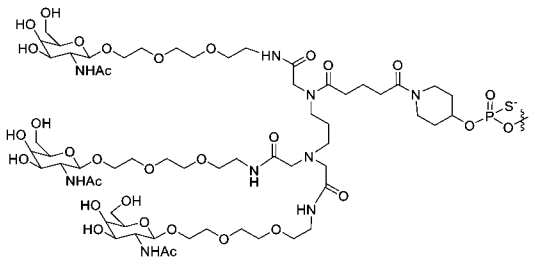
n"獨立地選自1或2。

【請求項34】 如請求項30至33中任一項所述的dsRNA藥劑，其中所述靶向基團具有以下結構：

 GLO-1	 GLS-1*
 GLO-2	 GLS-2*
 GLO-3	 GLS-3*
 GLO-4	 GLS-4*
 GLO-5	 GLS-5*

 GLO-6	 GLS-6*
 GLO-7	 GLS-7*
 GLO-8	 GLS-8*
 GLO-9	 GLS-9*
 GLO-10	 GLS-10*

 GLO-11	 GLS-11*
 GLO-12	 GLS-12*
 GLO-13	 GLS-13*
 GLO-14	 GLS-14*
 GLO-15	 GLS-15*

 GLO-16	 GLS-16*

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【請求項35】 如請求項1至34中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含與所述有義鏈的5'-末端綴合的靶向基團。

【請求項36】 如請求項1至34中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含與所述有義鏈的3'-末端綴合的靶向基團。

【請求項37】 如請求項1至34中任一項所述的dsRNA藥劑，其中所述反義鏈包含在3'-末端處的一個反向無鹼基殘基。

【請求項38】 如請求項1至34中任一項所述的dsRNA藥劑，其中所述有義鏈包含在3'或/和5'末端處的一個或兩個反向無鹼基殘基或異甘露醇殘基。

【請求項39】 如請求項1至38中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑包含在所述有義鏈的5'末端處的一個反向無鹼基殘基或異甘露醇殘基，其中所述反向無鹼基殘基或異甘露醇殘基經由硫代磷酸酯鍵與所述有義鏈的所述核苷酸序列的所述5'末端的相鄰核苷酸連接；和/或所述dsRNA藥劑包含在所述有義鏈的3'末端處的一個反向無鹼基殘基或異甘露醇殘基，其中所述反向無鹼基殘基或異甘露醇殘基經由硫代磷酸酯鍵與所述有義鏈的所述核苷酸序列的所述3'末端的相鄰核苷酸連接 。

【請求項40】 如請求項39所述的dsRNA藥劑，所述有義鏈還包含與有義鏈5'末端處的反向無鹼基殘基或異甘露醇殘基連接的靶向基團，其中所

述靶向基團經由硫代磷酸酯鍵與相鄰的反向無鹼基殘基或異甘露醇殘基連接，並且任選的靶向基團是N-乙醯基-半乳糖胺（GalNAc）。

【請求項41】 如請求項1至40中任一項所述的dsRNA藥劑，其中所述dsRNA藥劑具有兩個平端。

【請求項42】 如請求項1至40中任一項所述的dsRNA藥劑，其中至少一條鏈包含至少1個核苷酸的3'突出端。

【請求項43】 如請求項1至42中任一項所述的dsRNA藥劑，其中至少一條鏈包含至少2個核苷酸的3'突出端。

【請求項44】 如請求項1至43中任一項所述的dsRNA藥劑，其中所述INHBE RNA轉錄本是SEQ ID NO: 1。

【請求項45】 一種組合物，其中所述組合物包含如請求項1至44中任一項所述的dsRNA藥劑。

【請求項46】 如請求項45所述的組合物，其中所述組合物還包含藥學上可接受的載劑。

【請求項47】 如請求項46所述的組合物，其中所述組合物還包含一種或多種另外的治療劑。

【請求項48】 如請求項47所述的組合物，其中所述組合物被包裝在試劑盒、容器、包裝件、分配器、預填充注射器或小瓶中。

【請求項49】 如請求項45至48中任一項所述的組合物，其中所述組合物被配製用於皮下施用，被配製用於鞘內施用，或者被配製用於靜脈內（IV）施用。

【請求項50】 一種細胞，所述細胞包含如請求項1至44中任一項所述的

dsRNA藥劑，任選地，所述細胞是哺乳動物細胞，任選地是人細胞。

【請求項51】 一種抑制細胞中INHBE基因的表達的方法，其中所述方法包括：

(i)製備包含有效量的如請求項1至44中任一項所述的雙鏈核糖核酸（dsRNA）藥劑或如請求項45至49中任一項所述的組合物的細胞。

【請求項52】 52.如請求項51所述的方法，其中所述方法還包括：

(ii)維持如請求項51所述的(i)中製備的所述細胞足夠長的時間以獲得INHBE基因的mRNA轉錄本的降解，從而抑制所述細胞中INHBE基因的表達。

【請求項53】 如請求項51至52中任一項所述的方法，其中所述細胞在受試者體內並且通過皮下或靜脈內（IV）將所述dsRNA藥劑施用於所述受試者。

【請求項54】 如請求項53所述的方法，所述方法包括在將所述dsRNA藥劑施用於所述受試者後評估對INHBE基因的抑制，其中用於所述評估的方式包括：

(i)測定所述受試者的INHBE相關疾病或病症的一種或多種生理特徵，以及

(ii)將所測定的生理特徵與所述INHBE相關疾病或病症的治療前基線生理特徵和/或所述INHBE相關疾病或病症的對照生理特徵進行比較，

其中所述比較表明對所述受試者體內INHBE基因表達的抑制存在或不存在中的一者或多者。

【請求項55】 如請求項54所述的方法，其中所測定的生理特徵是以下

中的一者或多者：所述受試者的INHBE mRNA水平、INHBE蛋白水平，或代謝障礙。

【請求項56】 如請求項55所述的方法，其中降低所述受試者的INHBE mRNA水平、所述受試者的INHBE蛋白水平中的一者或多者，和/或降低根據體重指數調整的腰臀比。

【請求項57】 一種抑制受試者中的INHBE基因的表達的方法，其中所述方法包括向所述受試者施用有效量的如請求項1至44中任一項所述的雙鏈核糖核酸（dsRNA）藥劑或如請求項45至49中任一項所述的組合物。

【請求項58】 如請求項57所述的方法，其中通過皮下、鞘內或靜脈內（IV）將所述dsRNA藥劑施用於受試者。

【請求項59】 如請求項57至58中任一項所述的方法，所述方法包括在施用所述dsRNA藥劑後評估對INHBE基因的抑制，其中用於所述評估的方式包括：

(i)測定所述受試者的INHBE相關疾病或病症的一種或多種生理特徵，以及

(ii)將所測定的生理特徵與所述INHBE相關疾病或病症的治療前基線生理特徵和/或所述INHBE相關疾病或病症的對照生理特徵進行比較，

其中所述比較表明對所述受試者體內INHBE基因表達的抑制存在或不存在中的一者或多者。

【請求項60】 如請求項59所述的方法，其中所測定的生理特徵是以下中的一者或多者：所述受試者的INHBE mRNA水平、INHBE蛋白水平、代謝障礙。

【請求項61】 如請求項60所述的方法，其中降低所述受試者的INHBE mRNA水平、所述受試者的INHBE蛋白水平中的一者或多者，和/或降低根據體重指數調整的腰臀比。

【請求項62】 一種治療與INHBE蛋白的存在相關的疾病或病症的方法，其中所述方法包括向受試者施用有效量的如請求項1至44中任一項所述的雙鏈核糖核酸（dsRNA）藥劑，或如請求項45至49任一項所述的組合物，以抑制INHBE基因表達。

【請求項63】 如請求項62所述的方法，其中所述疾病或病症是以下中的一者或多者：代謝障礙，諸如2型糖尿病、肥胖症（特別是腹部肥胖症）、脂肪代謝障礙（諸如無法在區域性脂肪庫中沉積脂肪（部分脂肪代謝障礙）或者無法在全身沉積脂肪（脂肪萎縮））、肝臟脂肪沉積或脂肪肝病及其併發症（諸如，例如肝硬化、纖維化或肝臟炎症）、高脂血症或血脂異常（低密度脂蛋白膽固醇（LDL-C）、甘油三酯、極低密度脂蛋白膽固醇（VLDL-C）、載脂蛋白B或其他脂質成分的循環水平高或改變）、肝酶水平或其他肝損傷標誌物（諸如，例如ALT和/或AST）較高或升高或改變、非酒精性脂肪性肝炎（NASH）、胰島素抵抗或者在空腹或代謝挑戰期間的胰島素水平較高或改變、其他類型的肝臟炎症和/或甘油三酯水平升高，和/或心血管疾病，諸如心肌病、心力衰竭，以及高血壓和/或高血壓症、血糖或葡萄糖較高或高血糖症、代謝症候群、冠狀動脈疾病和其他冠狀動脈粥樣硬化病症，以及上述病症中的每一者的併發症。

【請求項64】 如請求項63所述的方法，所述方法還包括向所述受試者施用另外的治療方案。

【請求項65】 如請求項64所述的方法，其中所述另外的治療方案包括：向所述受試者施用一種或多種本發明的INHBE反義多核苷酸，向所述受試者施用非INHBE dsRNA治療劑，以及對所述受試者的行為矯正。

【請求項66】 如請求項65所述的方法，其中所述非INHBE dsRNA治療劑是以下中的一者或多者：二甲雙胍、胰島素、格列本脲、格列吡嗪、格列美脲、瑞格列奈、那格列奈、噻唑烷二酮、羅格列酮、吡格列酮、西他列汀、沙格列汀、利格列汀、艾塞那肽、利拉魯肽、司美格魯肽、卡格列淨、達格列淨和恩格列淨、芬特明、托吡酯、安非他酮、納曲酮、利拉魯肽、瑞舒伐他汀、辛伐他汀、阿托伐他汀、非諾貝特、吉非貝齊、非諾貝酸、尼克酸、ω-3脂肪酸、替莫瑞林、聚-L-乳酸、羥基磷灰石鈣、聚甲基丙烯酸甲酯、牛膠原蛋白、人膠原蛋白、矽酮、透明質酸、肝炎治療劑、肝炎疫苗、阿托伐他汀、氟伐他汀、洛伐他汀、匹伐他汀、普伐他汀、瑞舒伐他汀鈣、辛伐他汀、考來烯胺、考來維侖、考來替泊、阿利西尤單抗、依洛尤單抗、煙酸、速釋煙酸、非諾貝特、吉非貝齊、貝培多酸、咖啡、葉酸、鉀、維生素B6、他汀類、奧貝膽酸、司隆色替、埃拉菲布拉諾、西尼昔洛韋、GR_MD_02、MGL_3196、IMM124E、二十烷醯胺基膽烷酸、GS0976、恩利卡生、Volixibat、NGM282、GS9674、卓匹非索、MN_001、LMB763、Bl_1467335、MSDC_0602、PF_05221304、DF102、沙羅格列紮、BMS986036、拉尼蘭諾、司美格魯肽、硝唑尼特、GRI_0621、EYP001、VK2809、納美芬、LIK066、MT_3995、依洛昔巴、納莫德森、福雷蘆單抗、SAR425899、索格列淨、EDP_305、艾考布特、吉卡賓、TERN_101、KBP_042 、 PF_06865571 、 DUR928 、 PF_06835919 、 NGM313 、

BMS_986171、那馬西佐單抗、CER_209、ND_L02_s0201、RTU_1096、DRX_065、IONIS_DGAT2Rx、INT_767、NC_001、司拉德帕、PXL770、TERN_201、NV556、AZD2693、SP_1373、VK0214、肝源性幹細胞、TGFTX4、RLBN1127、GKT_137831、RYI_018、CB4209-CB4211、JH_0920、氯噻酮、氯噻嗪、氫氯噻嗪、吲達帕胺、美托拉宗、醋丁洛爾、阿替洛爾、倍他洛爾、富馬酸比索洛爾、鹽酸卡替洛爾、酒石酸美托洛爾、琥珀酸美托洛爾、納多洛爾、鹽酸貝那普利、卡托普利、馬來酸依那普利、福辛普利鈉、賴諾普利、莫昔普利、培哚普利、鹽酸喹那普利、雷米普利、群多普利、坎地沙坦、甲磺酸依普沙坦、厄貝沙坦、洛沙坦鉀、替米沙坦、纈沙坦、苯磺酸氨氯地平、苄普地爾、鹽酸地爾硫卓、非洛地平、伊拉地平、尼卡地平、硝苯地平、尼索地平、鹽酸維拉帕米、甲磺酸多沙唑嗪、鹽酸哌唑嗪、鹽酸特拉唑嗪、甲基多巴、卡維地洛、鹽酸拉貝洛爾、α甲基多巴、鹽酸可樂定、乙酸胍那苄、鹽酸胍法辛、胍那決爾、單硫酸胍乙啶、利血平、鹽酸肼屈嗪、米諾地爾、ACE抑制劑、血管緊張素II受體阻斷劑、β阻斷劑、鈣通道阻斷劑、抗心律失常藥、醛固酮阻斷劑、利尿劑、抗凝血劑、血液稀釋劑、皮質類固醇、鹽皮質激素受體拮抗劑、利尿劑、伊伐佈雷定、沙庫巴曲纈沙坦、硝酸鹽肼屈嗪和地高辛。

【請求項67】 如請求項62至66中任一項所述的方法，其中通過皮下、鞘內或靜脈內（IV）將所述dsRNA藥劑施用於所述受試者。

【請求項68】 如請求項62至67中任一項所述的方法，所述方法還包括測定所施用的雙鏈核糖核酸（dsRNA）藥劑對所述受試者的功效。

【請求項69】 如請求項68所述的方法，其中測定對所述受試者的治療

功效的方式包括：

(i)測定所述受試者的INHBE相關疾病或病症的一種或多種生理特徵，以及

(ii)將所測定的生理特徵與INHBE相關疾病或病症的治療前基線生理特徵進行比較，

其中所述比較表明向受試者施用的雙鏈核糖核酸（dsRNA）藥劑的存在、不存在和功效水平中的一者或多者。

【請求項70】 如請求項69所述的方法，其中所測定的生理特徵是：所述受試者的INHBE mRNA水平、INHBE蛋白水平，或代謝障礙。

【請求項71】 如請求項70所述的方法，其中降低所述受試者的INHBE mRNA水平、INHBE蛋白水平中的一者或多者，和/或降低根據體重指數調整的腰臀比。

【請求項72】 一種與受試者的INHBE蛋白的基線治療前水平相比降低所述受試者的INHBE蛋白水平的方法，其中所述方法包括向所述受試者施用有效量的如請求項1至44中任一項所述的雙鏈核糖核酸（dsRNA）藥劑或如請求項45至49中任一項所述的組合物，以降低INHBE基因表達水平。

【請求項73】 如請求項72所述的方法，其中通過皮下、鞘內或靜脈內（IV）將所述dsRNA藥劑施用於所述受試者。

【請求項74】 一種與受試者的INHBE相關疾病或病症的治療前基線生理特徵相比改變所述受試者的INHBE相關疾病或病症的生理特徵的方法，其中所述方法包括向所述受試者施用有效量的如請求項1至44中任一項所述的雙鏈核糖核酸（dsRNA）藥劑或如請求項45至49中任一項所述的組合

物，以改變所述受試者的INHBE相關疾病或病症的生理特徵。

【請求項75】 如請求項74所述的方法，其中通過皮下、鞘內或靜脈內（IV）將所述dsRNA藥劑施用於所述受試者。

【請求項76】 如請求項75中任一項所述的方法，其中所述生理特徵是以下中的一者或多者:所述受試者的INHBE mRNA水平、INHBE蛋白水平，或代謝障礙。